Cannabis Use, Drug-Drug and Drug-Disease Interactions in Older Patients

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Abstract

AIM: The aim of this research was to find out whether medical cannabis or the combination with common drugs or diseases lead to still unknown side effects or interactions in older adults.

BACKGROUND: Medical cannabis is becoming more and more important, with increasing consumption being noted in the older population (Han et al., 2017). Older adults are particularly susceptible to drug adverse events due to their altered physiology (Grundy et al., 2001; Khaw, 1997; Le Couteur et al., 2005; Mangoni & Jackson, 2003; Rochon & Gurwitz, 1997), increased likelihood of illnesses (Niccoli & Partridge, 2012) and high number of prescribed drugs (Qato et al., 2008). However, since there are hardly any clinical studies on medical cannabis, especially not in geriatric patients, pharmacovigilance plays a very important role.

METHODS: FAERS (FDA Adverse Event Reporting System), a large pharmacovigilance database, was used as data source. Cannabis case reports of patients being 50 years and older have been extracted, cleaned, sorted, and analyzed. Afterwards, received data were compared with data already known from literature.

RESULTS: The results have shown the conditions under which cannabis products have been taken by people over 50 years and what adverse events this led to. Further analysis of individual case reports highlighted the importance of both pharmacokinetic and pharmacodynamic interactions of cannabis. In addition to this descriptive analysis, a list of drugs that potentially interact with CBD, THC or nabiximols has been created. Statistical calculations and analysis of drug-disease interactions could not be carried out due to a lack of data in FAERS.

CONCLUSION: This thesis does not only describe the importance of medical cannabis in older patients by demographic analysis, but also provides information on possible drug combinations with cannabis, which are potentially harmful in the older generation. It therefore makes sense in future clinical studies to rule out interactions in order to ensure the safe use of medical cannabis in older adults.

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1 Introduction

1.1 General Information about Cannabinoids

The cannabis plant, Cannabis sativa subsp. indica or Cannabis sativa subsp. sativa, consists of over 500 plant constituents, which represent almost all chemical classes, e.g. steroids, flavonoids, monoterpenes, sesquiterpenes, amino acids, among others (Elsohly et al., 2017; Elsohly & Slade, 2005). Cannabinoids are particularly noteworthy here, as this group of plants play a major role in the pharmacological effects of the human body. About 70 cannabinoids are known, the most important of which are probably CBD and THC (Elsohly & Slade, 2005). Both substances are of great importance not only for recreational but also for medical purposes. However, most of the data on effects, side effects and interactions that are known or reported to pharmacovigilance systems come from people who use cannabis recreationally, since cannabis products have not been approved for a long time and clinical studies are therefore very limited. Already known information, whether it concerns recreational or medical use, is presented in the following chapters.

1.1.1 Cannabinoid Targets

In order to better understand the diverse effects of CBD and THC, one must first of all take a closer look at the cannabinoid targets and their localization. The main receptors of cannabinoids are CB1 and CB2 receptors, the receptors of the body's own endocannabinoids.

CB1 receptors play an essential role in the psychotropic effects of cannabis since they are primarily found in brain areas like hippocampus (responsible for memory), amygdala (emotional responses), cerebral cortex (cognition), limbic forebrain (motivation) and cerebellum (motor coordination) (Castle et al., 2012; Huestis et al., 2001). The medullary nuclei, a specific part of the brain that influences respiratory and cardiovascular functions, contains less cannabinoid receptors. This could be a reason why high doses of THC do not cause any death (Herkenham et al., 1990). However, CB1 receptors can also be found in small amounts in the testis, heart, immune cells and vascular tissue (Brown, 2007). CB2 receptors are primarily located on immune cells and hematopoietic cells (Galiègue et al., 1995). Together with cannabinoids or endocannabinoids those receptors play a major role in the regulation of the immune system (Cabral & Griffin-Thomas, 2009). Peripheral tissues like gastrointestinal

tract, cardiovascular system, bone, adipose tissue and reproductive system do also contain CB2 receptors, though (Howlett et al., 2002).

THC mainly interacts with CB1 receptors but also sometimes with CB2 receptors as partial agonist, whereas CBD acts as an antagonist of CB1 and CB2 receptor agonists with low affinity (Pertwee, 2008).

However, cannabinoids also have other targets than CB receptors. For example, Ibeas Bih et al. summarized over 65 molecular targets of CBD mentioned in literature, namely adenosine A1/A2 receptors, opioid receptors, serotonin receptors, G-protein-coupled-receptor 55, nicotinic acetylcholine receptor, peroxisome proliferator activated receptor, among others. (Ibeas Bih et al., 2015). CBD and THC also interact with various enzymes, further described in chapter pharmacokinetics (see chapter 1.1.3 Enzymes and Transporters that interact with Cannabinoids). In addition, two orphan G-protein-coupled-receptors, namely GPR119 and GPR55, which are potential targets of cannabinoids (McHugh et al., 2010; Ryberg et al., 2007), will remain in the interests of research (Brown, 2007).

The activation or inhibition of these receptors by CBD or THC has a great impact on various areas in the body, which are described below.

1.1.2 Effects

The effects of both, recreational and medical cannabis have been described in the next chapters. Data on recreational cannabis were taken into account due to the lack of studies on medically approved cannabis products.

Since the targets of cannabinoids are variable, so are the effects and side effects caused by cannabinoids. It must also be borne in mind that people have their individual sensitivity to cannabis and therefore different probabilities for reactions (Atakan, 2012).

1.1.2.1 Desired Effects

Cannabis is a drug that has been used for many years for its desirable effects. Medicinally, it is mainly used for chronic pain, epilepsy, nausea, vomiting, seizures, cancer, inflammatory diseases (e.g. Crohn's disease), muscle spasms, Alzheimer's disease, Parkinson's disease, HIV and AIDS (Drugs.com, 2020a; Greenwich Biosciences, Inc., 2020; GW Pharma Ltd., 2019; National Conference of State Legislatures, 2020; Patheon Softgels Inc., 2017; Valeant Pharmaceuticals International, 2006). Due to its wide range of uses, some studies have taken

a closer look at the efficacy and safety of medicinal cannabis, which are summarized and analyzed from Amato et al. Cannabis is considered safe and efficient in 15 studies on multiple sclerosis, 12 studies on chronic pain, two studies on Tourette syndrome and dementia and 14 studies on cancer. However, some of those studies report their financial dependence on pharmaceutical companies, which probably had an impact on the study results (Amato et al., n.d.).

When describing medicinal cannabis, it is important to differentiate between CBD and THC products, since both ingredients differ in their indications and effects.

Looking closer at the effects of THC, it is noticeable that it acts mainly in the brain due to the primary effect on CB1 receptors (Castle et al., 2012; Huestis et al., 2001). There it leads to various reactions. First, the antiemetic property of THC needs to be mentioned. A study compared THC with prochlorperazine, both of which are used to treat chemotherapy-induced nausea and vomiting. THC and prochlorperazine are classified as being equally effective. Although cannabis had a higher potential for side effects, it was still preferred to prochlorperazine (Ungerleider et al., 1982). The high density of CB1 receptors in the forebrain and cerebellum (Castle et al., 2012) indicates that cannabinoids are of great importance in movement and cognition. For example, it should help well with tremor or spasticity (Clifford, 1983; Petro & Ellenberger, 1981). An example for a medically approved preparation containing synthetically produced THC is Cesamet, which is used for the treatment of chemotherapy-induced nausea and vomiting when conventional medication is ineffective (Valeant Pharmaceuticals International, 2006). Marinol, also a THC analogue, is approved for the same indication but also for weight loss due to anorexia in AIDS patients (Patheon Softgels Inc., 2017).

CBD causes other effects in the human body, which is why the indications differ from those of THC. CBD has antiarrhythmic effects due to activation of adenosine A1 receptors, which are important receptors in the heart (Gonca & Darıcı, 2015). It is also said to interact with adenosine A2 receptors, which might lead to anti-inflammatory effects (Ibeas Bih et al., 2015; Liou et al., 2008; Mecha et al., 2013). These anti-inflammatory properties could be used in autoimmune diseases. Furthermore, CBD has antiepileptic (Cunha et al., 1980), anxiolytic (Fusar-Poli et al., 2009), antipsychotic (Ghabrash et al., 2020), antispastic (Wade et al., 2004) and analgetic (Urits et al., 2019; Wade et al., 2004) properties, that can be used medicinally. An approved preparation that contains CBD is Epidiolex, which is indicated for the treatment

of special forms of epilepsy, namely Lennox-Gastaut syndrome or Dravet syndrome (Greenwich Biosciences, Inc., 2020).

The combination of THC and CBD is also used because the effects mutually influence each other. CBD can curb the hallucinogenic properties of THC, that are regarded as side effects. It has been discovered that the toxicity of cannabis is higher when low doses of CBD are combined with THC, whereas the toxicity is lower when high doses of CBD are combined with THC (Solowij et al., 2019). A pharmacokinetic interaction tends to be ruled out though. (Karschner et al., 2011) These considerations are important for both medical and recreational use. Since the two cannabinoids CBD and THC have an impact on each other, it is important to examine the combination of both cannabinoids separately in the thesis, as far as data are available. There is also a medicinal product on the market, that contains a combination of equal parts of CBD and THC. It is called Sativex and it is medically approved for spasms in multiple sclerosis (GW Pharma Ltd., 2019).

1.1.2.2 Adverse Side Effects

Cannabinoids can cause a wide variety of side effects throughout the body. First and foremost, side effects that have been found in studies as part of the approval of medical cannabis products, are listed.

Cesamet, which contains the synthetic THC analogue nabilone, might lead to some notable side effects on the central nervous system. Those include psychological dependence, depression, anxiety, and panic attacks. The drug might have a negative impact on cognition and memory as well. Hallucinations are also observed, albeit at higher doses. Acute side effects, for which tolerance is quickly developed, are relaxation, euphoria, and drowsiness. Systemic side effects such as dry mouth and hypotension are also described (Valeant Pharmaceuticals International, 2006).

Another cannabis product is Marinol, which contains dronabinol as an active substance. Like nabilone, dronabinol is a synthetic THC analogue. The most common side effects (over 3%) include dizziness, euphoria, nausea, vomiting, abnormal thinking, somnolence, and abdominal pain. Cardiovascular side effects such as palpitations and tachycardia are also observed, although less frequently (Patheon Softgels Inc., 2017).

Epidiolex is the only medically approved cannabis product on the market that contains CBD in pure form. It often leads to side effects such as somnolence, diarrhea, fatigue, malaise, transaminase elevations, decreased appetite, insomnia, asthenia, sleep disorder, and infections (Greenwich Biosciences, Inc., 2020).

In the prescribing information on Sativex, a cannabis product that contains equal amounts of CBD and THC, physical and psychological dependence and cardiovascular effects like tachycardia, changes in blood pressure and postural hypotension are described as the most important side effects, which is why it is not recommended for people with existing cardiovascular disease or people with psychotic disorders. Long-term application of Sativex in multiple sclerosis patients showed palpitations, oral mucosal disorder, stomatitis, hypertension, syncope, and other side effects (GW Pharma Ltd., 2019). However, there is hardly any data on long-term side effects of medically approved cannabis products in general.

Due to many years of research on recreational cannabis, not only acute side effects but also long-term side effects can be described. It therefore makes sense to orientate on studies on recreational cannabis to get an idea of long-term side effects of medical cannabis.

Long-term effect means that cannabis is consumed almost daily for a longer period of months or years (World Health Organization, 2016). It can be assumed that long-time use leads to impairments in cognition and memory because the number of CB1 receptors in the brain, that are in charge of these brain functions, are downregulated (Villares, 2007). Studies claim that long-time use also leads to change of cannabinoid receptors on immune cells (Nong et al., 2002) and squamous cell carcinoma of head and neck (Donald, 1986).

Animal studies can also provide indications of long-term side effects. An animal study on albino rats has shown interesting results that could be of interest for future studies on humans. It was found that the bleeding time, platelet count and prothrombin time was significantly higher when taking cannabis chronically (Obembe et al., 2015).

In any case, it must be clarified if cannabis was taken as a consequence of a poor state of health or if cannabis is indeed the cause of the health problem. For example, it can either be assumed that someone got depression from using cannabis or it can be assumed that someone who already suffers from depression uses cannabis as self-medication against the disease. That is why statements like ‘cannabis increases the likelihood of depression’ have to be assessed carefully (World Health Organization, 2016).

1.1.2 Enzymes and Transporters that Interact with Cannabinoids

CBD interacts with a broad spectrum of enzymes and transporters. It acts as an inhibitor of Cytochrome P450 enzymes such as CYP1A1, CYP1A2, CYP1B1 (Yamaori et al., 2010), CYP2A6, CYP2B6 (Yamaori, Maeda et al., 2011), CYP2C9 (Yamaori et al., 2012), CYP2C19 (Jiang et al., 2013), CYP2D6 (Yamaori, Okamoto et al., 2011), CYP3A4, CYP3A5, CYP3A7 (Yamaori, Ebisawa et al., 2011), CYP2J2 (Arnold et al., 2018), CES1 (Qian, Wang, & Markowitz, 2019), UGT1A9, UGT2A7 (Al Saabi et al., 2013), MRP1/ABCC1 (Holland et al., 2008) and BCRP (Holland et al., 2007). However, it is not only an inhibitor but also a substrate of CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 (Jiang et al., 2011). The interaction with P-Gp is not clear yet. One study says that CBD has no effect on P-Gp (Holland et al., 2006), while another study shows that CBD inhibits P-Gp at a certain concentration (Zhu et al., 2006). Most likely, the concentration of CBD has an influence on the resulting effect.

THC has similar but not the same interactions. It acts as an inhibitor of CYP1A1, CYP1B1 (Yamaori et al., 2010), CYP2A6, CYP2B6 (Yamaori, Maeda et al., 2011), CYP2C9 (Yamaori et al., 2012), CYP2D6 (Yamaori, Okamoto et al., 2011), CYP3A4, CYP3A5, CYP3A7 (Yamaori, Ebisawa et al., 2011), CYP2J2 (Arnold et al., 2018), CES1 (Qian, Wang, & Markowitz, 2019), MRP1/ABCC1 (Holland et al., 2008) and BCRP (Holland et al., 2007). Regarding CYP2C9, one research group found that THC and its two metabolites 11-hydroxy-delta-9-THC and 11-nor-9-carboxy-delta-9-THC induce CYP2C9 (Bland et al., 2005), whereas another research group shows inhibition (Yamaori et al., 2012). The reasons for this could be a concentration-dependent effect and the use of different substrates.

The following interactions are listed in the prescribing information of cannabis products. The information mostly corresponds to the data mentioned above. However, there are slight differences, which on the one hand can be due to the fact that other cell cultures were used and on the other hand that the concentration of the substances has an influence on whether an interaction is clinically relevant or not.

Nabilone, the active ingredient of Cesamet and synthetic THC-analogue, does not significantly inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6 and CYP3A4 when midazolam and nifedipine are used as substrates. However, it has a weak inhibitory effect on CYP2E1 and CYP3A4 when testosterone is used as a substrate and a moderate inhibitory effect on CYP2C8 and CYP2C9 (Valeant Pharmaceuticals International, 2006).

Dronabinol, the active substance of Marinol, is primarily metabolized by CYP2C9 and CYP3A4, which is known from in vitro data (Patheon Softgels Inc., 2017).

More pharmacokinetic data are described for Epidiolex, which contains CBD as active ingredient. It is said to be metabolized mainly in the liver by CYP2C19, CYP3A4, UGT1A7, UGT1A9 and UGT2B7. Furthermore, it plays a role in inhibiting enzymes like CYP2C8, CYP2C9, CYP2C19, UGT1A9 and UGT2B7. With two enzymes, namely CYP1A2 and CYP2B6, it is not certain whether CBD induces or inhibits them. The CBD metabolite 7-COOH-CBD is not only a substrate of P-Gp but also an inhibitor of BCRP and BSEP (Greenwich Biosciences, Inc., 2020).

Sativex, the cannabis product that contains CBD as well as THC, is mainly metabolized by Cytochrome P450 and UGT enzymes, including CYP1A2, CYP2C9, CYP2D6, CYP2C19, CYP3A4, UGT1A9 and UGT2B7 (GW Pharma Ltd., 2019).

A more detailed overview of the already known interactions of cannabinoids is presented well in the paper from Qian, Gurley & Markowitz, 2019 (Qian, Gurley, & Markowitz, 2019).

All enzymes mentioned above are responsible for around three quarters of the metabolism of common drugs. These enzymes can exist in different genetic diversity and polymorphisms. It is therefore important to keep in mind that the metabolism of drugs can vary from person to person (Zanger & Schwab, 2013).

1.1.4 Interactions

1.1.4.1 Drug-Drug Interactions

Since not only cannabinoids interact with the beforementioned enzymes and transporters, one can assume several pharmacokinetic interactions with other drugs as well. If one of two co-administered drugs is an inhibitor and the other one a substrate of a specific enzyme, the concentration of the substrate will increase. On the contrary, the concentration decreases, if an inductor is present instead of an inhibitor. If both substances are substrates of the enzyme, they can displace each other from the enzyme's binding pocket, provided they bind in the same active site of the enzyme.

Caution should therefore be taken with all drugs that are inhibitors, inductors or substrates of cannabinoid relevant enzymes and transporters (chapter 1.1.3) if taken together with cannabis products. Some researchers describe theoretically possible interactions that have often not been clinically tested yet but might be interesting for future investigations. A good

overview of the potential interactions of CBD and THC with other common medications based on current knowledge is summarized in other papers and presented again in table 1 and table 2 (Brown, 2020, p. 5; Brown & Winterstein, 2019, p. 5, p. 7). These common drugs frequently have cannabis-related indications like epilepsy and cancer, which is why they are often used in combination with cannabinoids.

Table 1. Potential Pharmacokinetic Drug-Drug Interactions of CBD.

Enzymes	Medication Examples	Effect/Recommendation
CYP3A4 substrates	Immunosuppressants, chemotherapeutics, antidepressants, antipsychotics, opioids, benzodiazepines, z-hypnotics, statins, calcium channel blockers, others	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
CYP3A4 inhibitors	Strong: protease inhibitors, ketoconazole, loperamide, nefazodone Moderate: amiodarone, verapamil, cimetidine, aprepitant, imatinib	Increased CBD bioavailability, possible increase in risk of adverse effects. Reduce CBD dose.
CYP3A4 inducers	Strong: enzalutamide, phenytoin Moderate: carbamazepine, topiramate, phenobarbital, rifampicin, efavirenz, pioglitazone	Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C19 substrates	Antidepressants, antiepileptics, proton pump inhibitors, clopidogrel, propranolol, carisoprodol, cyclophosphamide, warfarin	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
CYP2C19 inhibitors	Strong: fluvoxamine, fluoxetine Other: proton pump inhibitors, cimetidine, ketoconazole, clopidogrel, fluconazole, efavirenz	Increased CBD bioavailability, possible increase in risk of adverse effects. Reduce CBD dose.
CYP2C19 inducers	Rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort	Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C8/9 substrates	Rosiglitazone, buprenorphine, montelukast, celecoxib, sulfonylureas, losartan, naproxen, phenobarbital, phenytoin, rosuvastatin, valsartan, warfarin	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
UGT1A9 substrates	Regorafenib, acetaminophen, canagliflozin, sorafenib, irinotecan, propofol, mycophenolate, valproic acid, haloperidol, ibuprofen, dabigatran, dapagliflozin, others	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity.

UGT2B7 substrates	Hydromorphone, losartan, ibuprofen, naproxen, ezetimibe, lovastatin, simvastatin, carbamazepine, valproate, others	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity.
BCRP substrates	Glyburide, imatinib, methotrexate, mitoxantrone, nitrofurantoin, prazosin, statins, dipyridamole	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity.
BSEP substrates	Paclitaxel, digoxin, statins, telmisartan, glyburide, ketoconazole, rosiglitazone, celecoxib	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity.

Involving key metabolism enzymes/transporters (Jiang et al., 2011) that convert CBD to its metabolites and enzymes/targets that could be affected by CBD (Brown & Winterstein, 2019, p. 5, p. 7). CYP= Cytochrome P450; UGT= uridine-5'-diphospho-glucoronosyltransferase; BCRP= breast cancer resistance protein; BSEP= bile salt export pump

Table 2. Potential Pharmacokinetic Drug-Drug Interactions of THC.

Enzymes	**Medication Examples**	**Effect/Recommendation**
CYP3A4 substrates	Immunosuppressants, antidepressants, antipsychotics, opioids, benzodiazepines, statins, many others	Increased substrate bioavailability, increased adverse effects of substrate
CYP3A4 inhibitors	Protease Inhibitors, ketoconazole, nefazodone, amiodarone, verapamil, cimetidine, imatinib, tamoxifen	Increased THC bioavailability, increased THC adverse effects
CYP3A4 inducers	Phenytoin, carbamazepine, topiramate, rifampicin, pioglitazone	Decreased THC bioavailability, decreased effectiveness
CYP2C9 substrates	Antidepressants, antiepileptics, proton pump inhibitors, warfarin	Increased substrate bioavailability, increased adverse effects of substrate
CYP2C9 inhibitors	Fluvoxamine, fluoxetine, proton pump inhibitors, ketoconazole, clopidogrel, fluconazole, fluorouracil	Increased THC bioavailability, increased THC adverse effects
CYP2C9 inducers	Rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort	Decreased THC bioavailability, decreased effectiveness
CYP2C19 substrates	Rosiglitazone, buprenorphine, montelukast, sulfonylureas, phenytoin, warfarin	Increased substrate bioavailability, increased adverse effects of substrate
CES1 substrates	Methylphenidate, cocaine, meperidine Pro-drugs: dabigatran, clopidogrel, simvastatin	Increased substrate bioavailability. Decreased pro-drug bioavailability.

Involving key metabolism enzymes that convert THC to its metabolites and enzymes/targets that could be affected by THC (Brown, 2020, p. 5). CYP= Cytochrome P450; CES1= Carboxylesterase 1

However, drug-drug interactions can take place not only in a pharmacokinetic but also in a pharmacodynamic way. If two administered substances produce the same effects or side

effects, they can potentiate each other and thus act synergistically. Since different drug-receptor-complexes might lead to similar reactions, the focus of this work is less on the receptor but more on the reaction. At the end of the day the effect or side effect is relevant. Therefore, receptors were not considered in the analysis of synergistic pharmacodynamic interactions.

Frequently reported side effects that occur with CBD are transaminase elevation, somnolence, sedation, decreased appetite, diarrhea, decreased weight, insomnia, gait disturbance, infections, and suicidal thoughts. Table 3 shows drugs with similar adverse effects, which might lead to synergistic pharmacodynamic interactions when combined with CBD (Brown & Winterstein, 2019, p. 8).

Table 3. Adverse Events of CBD and Other Drugs with Similar Reactions.

Adverse Events	Other Medications with Similar ADE
Transaminase elevation	Alcohol, acetaminophen, sulfonamides, antifungals, ACE inhibitors, antipsychotics
Somnolence, sedation, lethargy, fatigue	Benzodiazepines, opioids, antidepressants, antiepileptics, antihistamines
Decreased appetite	Stimulants, antibiotics, chemotherapies, antiretrovirals, some antidepressants
Diarrhea	Metformin, antibiotics, chemotherapy, proton pump inhibitors, antidepressants
Weight decreased	Stimulants, antibiotics, chemotherapies, antiretrovirals, some antidepressants
Insomnia, sleep disturbance	Antidepressants, dopamine agonists, stimulants, antiepileptics, steroids, diuretics, beta-blockers
Gait disturbance	Benzodiazepines, opioids, antidepressants, antiepileptics, antihistamines, antihypertensives, antiarrhythmics, sedatives/hypnotics, anticholinergics
Infections, pneumonia, viral infections	Corticosteroids, tumor necrosis factor inhibitors, non-steroidal anti-inflammatory drugs, chemotherapy
Suicidal thoughts or behaviors	Antihypertensives, antidepressants, hormones, anxiolytics, analgesics, respiratory agents, anticonvulsants

Adverse events of CBD are also reported with other medications. Some examples are listed in the right column (Brown & Winterstein, 2019, p. 8).

The main adverse effects of THC are neuropsychiatric side effects like anxiety and depression, impaired cognition like sedation, increased infection risk and cardiovascular effects like hypertension and tachycardia. Caution should be taken with drugs that have similar effects, since those effects might potentiate each other (Brown, 2020).

It is assumed that cannabinoids and opioids act synergistically because they produce similar effects such as antinociception, sedation, hypotension, and inhibition of intestinal mobility. In one study, the combination of morphine or oxycodone was measured together with vaporized cannabis. Pharmacokinetic interactions could not be determined, but synergistic pharmacodynamic effects are believed to have led to improved pain relief (Abrams et al., 2011).

Most of the above-mentioned interactions are not clinically confirmed. Therefore, clinical studies are needed to verify presumed interactions. However, some clinical studies about drug-drug interactions of cannabinoids exist. Drug combinations that interact with each other are CBD-clobazam (Geffrey et al., 2015), CBD-topiramate, CBD-rufinamide, CBD-eslicarbazepine, CBD-zonisamide, CBD-valproate (Gaston et al., 2017), CBD-ketoconazole, THC-ketoconazole, CBD-rifampicin, THC-rifampicin (Stott et al., 2013), CBD-clobazam, CBD-stiripentol (Morrison et al., 2019), CBD-hydroxymidazolam (major metabolite of midazolam) (Morrison et al., 2018), THC-risperidone (Brzozowska et al., 2017), CBD-fluconazole, THC-fluconazole (GW Pharma Ltd., 2019), CBD-oseltamivir and THC-oseltamivir (Qian, Wang, & Markowitz, 2019). The interaction between cannabinoids and warfarin is not yet fully understood. However, patients taking warfarin are cautioned not to use cannabis (Damkier et al., 2019).

Interactions between some drug combinations were ruled out. For example, it is known that medicinal cannabis does not affect the pharmacokinetics of irinotecan and docetaxel (Engels et al., 2007) and that fentanyl has not influence on the plasma level of CBD (Manini et al., 2015). Furthermore, there is not any change of pharmacokinetic parameters when CBD or THC is co-administered with omeprazole (Stott et al., 2013). The antipsychotic action of clozapine is not affected by THC neither, which is why this drug is preferred to risperidone in schizophrenia patients who consume cannabis (Brzozowska et al., 2017). When looking at the prescribing information of Sativex (GW Pharma Ltd., 2019) and Cesamet (Valeant Pharmaceuticals International, 2006), no drug-drug interactions have been seen when taking it at clinical doses together with other drugs. Marinol's prescribing information states that the induction and inhibition potential of dronabinol, the active ingredient of Marinol, is not yet fully understood because no formal drug-drug interaction studies have been carried out with dronabinol (Patheon Softgels Inc., 2017).

1.1.4.1 Drug-Disease Interactions

Cannabinoids might also have an impact on underlying diseases. With the background knowledge that cannabinoids, especially THC, may lead to cardiovascular side effects (Patheon Softgels Inc., 2017), it is very likely that these effects can exponentiate in patients who already suffer from an underlying cardiovascular disease. But not only synergistic pharmacodynamic effects play a role here. Patients who have problems with the cardiovascular system are often already on drugs that can in turn interact pharmacokinetically with cannabis. One study that has examined the potential associations in between cannabis consumption and cardiovascular risks. Although the level of evidence is not constant, it is estimated that over two million U.S. citizens, who have ever used cannabis, suffer from cardiovascular diseases (DeFilippis et al., 2020). Hence, patients with high cardiovascular risk should be warned to not use cannabis.

Since cannabinoids have a huge impact on the immune system (Ibeas Bih et al., 2015; Liou et al., 2008; Mecha et al., 2013), they play a major role in infectious diseases as well. Cannabinoids affect different infectious agents, by allowing their replication or by eliminating them. In the review by Hernández-Cervantes, the possible role of cannabis in the presence of sepsis or infection with various bacteria or viruses, parasites or fungi is described. Not much data is available on this yet. However, the importance of the studies described is definitely given because cannabis receptors are present on immune cells, which in turn are responsible for the elimination of antigens (Hernández-Cervantes et al., 2017).

The influence of CBD on neurological diseases has not been fully clarified yet. It is very unlikely that CBD has an impact on neurological diseases through the endocannabinoid system. Although there is no evidence so far, some molecular targets of CBD could play a role in psychiatric diseases. For example, in epilepsy VDAC1 (voltage-dependent anion channel 1), in movement disorders CaV3.x, in neurodegenerative diseases FABP (fatty acid binding protein), with pain TRPV1 (transient receptor potential vanilloid type 1), in psychosis 5-HT1A and for addiction opioid receptors can be influenced by CBD, often by changing the intracellular calcium concentration (Ibeas Bih et al., 2015). These molecular targets should therefore be investigated more closely.

Another study found that although both cannabis and personality disorder have an increased likelihood of psychiatric comorbidity, a combination of the two does not increase the odds of

incident psychiatric comorbidities. These odds are sometimes even reduced (Shalit et al., 2019).

Some data clearly show the importance of warning patients with a certain underlying disease to not use cannabis. For example, schizophrenia patients should avoid using cannabis, because the consumption of cannabis with a high THC content even favors “an earlier onset of psychosis” (Di Forti et al., 2014, p. 1509). However, recreational cannabis is frequently consumed by schizophrenia patients (Myles et al., 2016).

It can also be assumed that in the case of renal or liver diseases, organs that play a major role in metabolism, the metabolism of cannabinoids is different and therefore the potential for side effects is even higher.

1.2 Medical Marijuana Use

The importance of cannabis in medicine has increased in recent years. Lin et al. looked at the 2013 National Survey on Drug Use and Health (NSDUH) data and found that in U.S. states where medical cannabis is legalized, 17% of adults using cannabis have used it medicinally. When comparing recreational and medical cannabis users, there are no differences in education, race, or occurrence of cannabis use disorder. However, it is noticeable that people who use cannabis medicinally suffer from poorer health conditions (Lin et al., 2016). In another paper it is shown, that especially people with COPD, asthma, arthritis, cancer and depression make use of medicinal cannabis (Dai & Richter, 2019).

In Canada, patients registered for the Marijuana for Medical Purposes Regulations (MMPR) program were asked about their cannabis use. It was found that 63% use cannabis as a substitute for prescription drugs, 30% of these used cannabis instead of opioids, 16% instead of benzodiazepines and 12% instead of antidepressants (Lucas & Walsh, 2017).

Even if the numbers of medicinal cannabis users are increasing, there are still limitations that prevent its optimal success. First, questions about efficacy, safety, dosage, indications and interactions remain to be fully resolved (Hill, 2019; Ziemianski et al., 2015). Second, in the training of doctors and pharmacists, cannabis tends to rank at the back and is rarely discussed. As a result, patients are not informed well about the possible use of cannabis, making it difficult for them to access it (Temple et al., 2019). Finally, cannabis still has the image of the bad, addictive and illegal drug in the minds of many people (Temple et al., 2019).

However, some people consider cannabis as a safe alternative to synthetic drugs because of its natural origin (Resko et al., 2019). This misjudgment is also known as natural fallacy.

Unfortunately, the inadequate data situation cannot be compensated by extrapolating recreational cannabis use, because the medically used oral cannabinoids have different chemical composition, type of application and dosage than smoked marijuana (Karst, 2018).

1.2.1 Cannabis Products

From a medical point of view, cannabis is approved for a wide variety of indications. Sativex (nabiximols) is indicated for cancer pain, neuropathic pain and spasticity in multiple sclerosis (GW Pharma Ltd., 2019), Cesamet (nabilone) for chemotherapy-induced nausea and vomiting (CINV) (Valeant Pharmaceuticals International, 2006), Marinol/Syndros (dronabinol) for CINV and anorexia with weight loss in AIDS patients (DPT Lakewood LLC, 2016; Patheon Softgels Inc., 2017), Epidiolex (CBD) for epilepsy (Greenwich Biosciences, Inc., 2020). More detailed information on the approved cannabis products can be found in table 4 (Brown, 2020, p. 3; Brown & Winterstein, 2019, p. 4). Why these indications have good evidence and which non-evidence-based indications exist are described elsewhere (Wong & Wilens Timothy E., 2017).

Table 4. Prescribed Cannabis Products.

Product (Approval Date)	Active Ingredient	Dosage Form	Route of Administration	Recommended Dose	Indication(s)
Epidiolex (2018)	Cannabidiol	Solution	Oral	2.5 mg/kg 2x daily; maintenance 5 mg/kg 2x daily; max 10 mg/kg 2x daily	Seizures associated with Lennox-Gastaut or Dravet syndrome
Marinol (1985)	Dronabinol (Synthetic-δ-9-THC)	Capsules	Oral	2.5 mg 2x daily; max 5 mg 2x daily 5 mg/m² 4-6x daily; max 15 mg/m² 4-6x daily	Anorexia associated with AIDS Nausea and vomiting with chemotherapy in patients for whom conventional treatment failed
Syndros (1985)	Dronabinol (Synthetic-δ-9-THC)	Capsules	Oral	2.1 mg 2x daily; max 8.4 mg daily 4.2 mg/m² 4-6x per day; max 12.6 mg/m² 4-6x per day	Anorexia associated with AIDS Nausea and vomiting with chemotherapy in patients for whom conventional treatment failed

Sativex (2011-12) not approved in the US	Nabiximols (δ-9-THC and CBD)	Solution, spray	Buccal spray	Titrated up to 12 sprays per day (patient median is 4-8 sprays) 2.7 mg THC and 2.5 mg CBD per spray	Adjunctive treatment of spasticity and neuropathic pain in multiple sclerosis Adjunctive analgesic for moderate to severe pain in advanced cancer

Product information for cannabis-derived medical products (Brown, 2020, p. 3; Brown & Winterstein, 2019, p. 4).

1.2.2 Cannabis Legalization

According to the World Drug Report 2019, cannabis is still the world's most widely consumed illegal drug with an estimated 188 million users in 2017 (United Nations Office on Drugs and Crime, 2019). However, the trend is going more towards legalization, which is why the medical use of cannabis is also becoming more and more important. The use of medicinal cannabis is regulated differently in the United States. 24 states have the comprehensive program, which allows CBD and THC use, 13 states have a restrictive program that limits the amount of THC in CBD products and four states have no cannabis program at all. In 11 states, even recreational cannabis consumption is legal (National Conference of State Legislatures, 2020). All in all, the number of legal medical marijuana patients in 26 out of 29 U.S. states is 2.132.777 (as of May 17th, 2018) (ProCon.org, 2018). The increase in medical cannabis use can be observed especially among older adults. From 2006/2007 to 2012/2013 the relative increase was 57.8% for adults between 50 and 64 years and 250% for adults over 65 years of age. Nevertheless, the prevalence in over 65 year old people is lower than in 50-64 year old people (1.4% in 2006/2008 vs. 7.1% in 2012/2013)(Han et al., 2017). One of the reasons why the users of medical cannabis are getting older is that people born between 1946 and 1964, the so-called baby boomer generation, have high rates of substance use and a positive attitude towards drug use due to personal exposure earlier in life (Blazer & Wu, 2009; Moore et al., 2009).

In a descriptive analysis of older adults (over 50 years of age) who were participants in a medical marijuana program in Florida, it was shown that this generation made up more than half of all early adopters of medical cannabis. For these, chronic pain and spasms were the most common indication (Brown et al., 2020). However, society is still divided about the use of medicinal cannabis. A survey on cannabis legalization in Michigan in 2016 showed that 48% were in favor of legalization, 42% against and 10% were unsure. The main argument against cannabis was the possible harm of cannabis. Cannabis advocates, however, have argued that

cannabis is less dangerous than other substances and medically valuable. Also, the state benefits financially from legal sales through levy taxes and lower costs due to lower crime rates (Resko et al., 2019).

Although the general trend towards medicinal cannabis is increasing, some researchers raise concerns about cannabis legalization. Legalization might lead to an even higher cannabis consumption and, in the long term, also might maximize potential damage to health, since potent cannabis products will be cheaper and easier to obtain in a legal state (Hall et al., 2019). Cerdá et al. examined in 2012 the correlation between medical cannabis legalization and cannabis use, abuse and dependence. As can be assumed, the odds of cannabis use, abuse and dependence were higher in states that legalized cannabis than in states where it is still considered an illegal drug (Cerdá et al., 2012).

1.3 Evaluation of Adverse Events and Interactions

Since medical cannabis is becoming more important, but there are still few clinical studies on side effects and interactions, pharmacovigilance is essential.

1.3.1 Pharmacovigilance

Pharmacovigilance is defined by the WHO as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems” (World Health Organization, 2002, p. 42).

In pharmacovigilance, drugs are still examined for side effects and interactions even after they have been approved. This is because many reactions cannot be observed before drug approval. In pre-clinical studies, you often only find a small number of test subjects and a wide variety of exclusion criteria, which means that certain patient populations such as older people are not taken into account at all. In addition, the duration of the study is often quite short. All of this speaks in favor of post-clinical studies. Further positive aspects of post-clinical studies are: First, rare reactions can be recorded. Second, the tolerability of drugs in high-risk patients, who are often excluded from studies, can be observed. Third, a longer investigation period is possible and fourth, many more potential drug-drug and food-drug interactions can be detected (U.S. Food and Drug Administration, 2016).

1.3.2 FAERS

The FDA Adverse Event Reporting System, shortly FAERS, is the FDA's post-marketing pharmacovigilance system, that is used since 1968. FAERS gathers case reports from spontaneous drug adverse events, that are reported worldwide by consumers (via the MedWatch website), health-care provider and pharmaceutical companies. This reporting system is also called MedWatch program. People, who are involved in the healthcare system are obliged to report any occurring side effect. The main goal of FAERS is to control the safety of drugs, that have been approved from the FDA. Identification of any safety concern by clinical reviewers leads to further evaluation process, additional studies, changes in prescribing information or even removal of the drug from the market (U.S. Food and Drug Administration, 2018). The case reports provide information about outcome (e.g. death, hospitalization), the reaction or adverse event, suspected drugs, concomitant drugs, reason for use (indication) and patient demographics like age, weight, and sex. Furthermore, information about reporting date and reporter type is available (U.S. Food and Drug Administration, 2020a). Reporting type, either consumer, pharmaceutical company, or healthcare professional, is important to prioritize events, since one can expect more detailed and reliable reports from healthcare providers than individual patients.

1.3.3 Safety Signal

A safety signal is present when a reported reaction is possibly related to a drug ingested but this connection is not known so far. It is only defined as a safety signal if other case reports show similar reactions and thus confirm the suspicion of a new side effect or interaction (U.S. Food and Drug Administration, 2016). In general, it is hard to say, how many reports form a new signal. Judgements are made based not only on the number, but also the quality of the case report, type of drugs, dosage etc.

Pharmacists are mostly responsible for reviewing the safety signals. They examine pharmacovigilance databases for frequently occurring events, so-called trends, and calculate statistical values in order to be able to make comparisons with other drugs. These trends are then analyzed more closely in complete case reports. The ultimate goal is to propose possible adverse drug reactions or drug-drug interactions of a certain medicinal substance (Sharrar & Dieck, 2013). Statistical analysis has proven to be very useful in detecting signals in spontaneous reporting systems (van Puijenbroek et al., 2002).

An example of post-clinical studies on cannabis has shown that cannabis-related cardiovascular side effects have risen steadily within five years. Cardiovascular side effects accounted for 2% of all reported cannabis incidents. This increase in reports was observed although it is known that side effects of cannabis are generally underreported (Jouanjus et al., 2011).

1.4 Application in the Field of Geriatrics

The population is getting older, so geriatrics is becoming more and more important. Older people generally suffer from more illnesses and therefore take more drugs than young people do (World Health Organization, 2020b). Adults over the age of 50 years are the most common users of prescribed drugs. 29% use five drugs or more, 42% at least one OTC product and 49% a dietary supplement (Qato et al., 2008). However, the more drugs are taken, the more drug interactions occur. It is estimated that the probability of at least one drug-drug interaction is 50% and in some population groups (patients over 60 years taking an antithrombotic and one or more additional long-term drug) it is even around 80% (Johnell & Klarin, 2007; Nobili et al., 2009; Schneider et al., 2018; Tulner et al., 2008).

Although geriatrics is important, there are only a few clinical studies that include the older generation. Even if clinical trials specialize in older people, frail old people are more likely to be an exclusion criterion. This leads to a very atypical healthy elderly group of test subjects and does not correspond to reality (McLean & Le Couteur, 2004). When looking at the prescribing information of all medically approved cannabis products, it is noted that limited data are available for drug use in older adults and one should therefore be very careful with the dosage administration in those people (Greenwich Biosciences, Inc., 2020; GW Pharma Ltd., 2019; Patheon Softgels Inc., 2017; Valeant Pharmaceuticals International, 2006). Even if clinical studies have not been conducted it is recommended that drug therapy should start slowly with a low dose. A reduced dose is intended to reduce side effects. However, reducing the dose is not always appropriate in older patients. For some drugs, it can be argued that a higher dosage is essential. For example, a higher dose of a broad-spectrum antibiotic is suitable for age-related immunosuppression (Le Couteur et al., 2004).

The changed physiology of older people also plays a role in drug application, which is explained in more detail in the following chapter.

1.4.1 Differences in Physiology of Older People

It is known that various functions in the body change during one's life course. Physiological processes show clear differences with age. Blood pressure and blood cholesterol rise, which leads to an increased risk of heart attacks and strokes. In addition, a reduced glucose tolerance and increased insulin resistance are observed, which promotes diabetes. Older people often have increased eye pressure, which can cause glaucoma and visual loss. Also, loss of bone mass and, as a result, increased fractures are observed. A reduced immune function, characterized by a declined activity of macrophages, neutrophils, natural killer cells, among others increases the risk of developing an infection or a specific tumor. In addition, neuronal degeneration is observed in old age, leading to reduced cognition and dementia (Gouin et al., 2008; Khaw, 1997). Changes in dopaminergic, serotonergic and glutamatergic systems, which are primarily the target of various drugs of abuse, and changes in hormone production (growth hormones, testosterones, estradiol) are known (Clegg et al., 2013; Dowling et al., 2008).

Age also has an influence on the metabolism and consequently the pharmacokinetics of drugs. Due to the reduced lean body mass, body water and total body volume the drug distribution decreases. Elimination processes via the kidneys are reduced, as well (Dowling et al., 2008). Not only the kidneys but also the liver as an important detoxification organ is restricted in its function, sometimes even about 30-50% (Le Couteur et al., 2005; Le Couteur & McLean, 1998; McLean & Le Couteur, 2004). More details on age-related changes in pharmacokinetics and pharmacodynamics are described elsewhere (Mangoni & Jackson, 2003).

These and many more changes in body functions in older people have a significant influence on the effects and side effects of substances such as cannabinoids. For example, in an animal study it was observed that THC is converted into the metabolite THC-COOH in the liver of adolescent mice twice as quickly as in the liver of adult mice. It was also noted that the brain of younger mice has higher m-RNA levels of BCRP. This multidrug transporter is responsible for the excretion of THC from the brain. The described observation could speak for a lower tolerance of THC in older mice and also apply to humans (Torrens et al., 2020). Another interesting theory has been made regarding the effects of cannabis on the aging brain. It is known that the brain changes continuously during life and is therefore composed slightly different in old age. How drugs such as cannabinoids affect the brains of old people is still not clear, but it is believed that cannabinoids have a positive influence on preventing specific diseases. They are supposed to prevent neurological damage caused by factors such as

glutamate, free radicals, reactive oxygen compounds and pro-inflammatory cytokines (Baker et al., 2003; Croxford, 2003; Fowler, 2003; Grundy et al., 2001; HAMPSON et al., 1998; HAMPSON et al., 2000; Lastres-Becker et al., 2002; Panikashvili et al., 2001). Due to this series of physiological changes, older people face an increased risk of serious drug-drug or drug-disease interactions.

1.4.2 Polypharmacy

Polypharmacy is defined by the WHO as "the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications. This includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient" (World Health Organization, 2019, p. 11).

Nowadays it is a very big challenge for physicians and pharmacists to reduce the large number of prescriptions to the most necessary drugs. The fewer the drugs, the better the tolerance and compliance. It also reduces the likelihood of interactions. In a study of older adults it was found that they take on average seven drugs. 46% of the observed population group take at least one drug combination that potentially leads to drug-drug interactions. Almost 10% of those possible drug-drug interactions were classified as avoidable (Björkman et al., 2002). Another risk factor for interactions is not only the number of drugs prescribed but also the number of physicians who are in the prescribing position. The more physicians are involved in the drug therapy of a patient, the greater the risk for a potential adverse drug interaction (Tamblyn et al., 1996).

Therefore the question of which drugs should be prescribed is becoming less relevant. Much more important is which drug can be removed from drug therapy.

But what exactly are the causes of polypharmacy? On the one hand people indeed suffer from various diseases, have various physicians and get various prescriptions. On the other hand, the so-called prescription cascade can also be the cause of multi-medication. Prescription cascade means that "an adverse drug reaction is misinterpreted as a new medical condition" (Rochon & Gurwitz, 1997, p. 1096). For example, a patient with an underlying disease is taken drug A. Drug A leads to side effect A and is then treated with drug B, which in turn leads to side effect B and so on. Attempts should be made to avoid these cascades, either by changing the drug immediately, changing the dosage or taking other medical measures in accordance with the guideline.

In a study, the influence of age on side effects was measured and something interesting was found. The likelihood of a type D (potentially serious) drug-drug interaction decreases with age, although the number of prescribed drugs increases. Future research is still necessary to understand these findings (Johnell & Klarin, 2007). Even if this connection is difficult to understand, it is still better news than expected.

1.4.3 Adverse Drug Events and Interactions in Older People

The prevalence of adverse drug events and interactions in older people is very high due to the reasons mentioned above such as changed physiology and polypharmacy. Adverse drug events are one of the most important reasons for hospitalization in the USA for people aged 65 or older. In the years 2004 to 2005 the most frequently involved drug classes with around 38.4% were “anticoagulants, insulins, opioid-containing analgesics, oral hypoglycemic agents, and antineoplastic agents” (Budnitz et al., 2006, p. 1862). Three drugs, namely warfarin, insulin and digoxin, accounted for almost a third of the emergency hospitalizations in older people due to adverse drug events (Budnitz et al., 2006). These data refer to the USA and cannot be applied one-to-one to Europe, as opioid use, for example, is more stringent in Europe. In a study with 674 older patients, 300 took more than one drug. 172 of these drug combinations led either to a side effect or to less effectiveness (Tulner et al., 2008). In another study with 5.077 older people, around 100 cases end up in emergency hospitalization due to adverse drug events. Four drugs or drug classes, namely warfarin, oral antiplatelet agents and oral hypoglycemic agents, were involved in 67% of all hospitalizations either alone or in combination (Budnitz et al., 2011).

If a side effect or an interaction occurs in an old person it is sometimes quite difficult to detect. Mostly unspecific reactions as fatigue or constipation appear, what can have a huge variety of aetologies (Lavan & Gallagher, 2016). In addition, side effects that occur in older people are often misinterpreted. For example, a side effect of a drug is often viewed as a symptom of an existing disease, a symptom of a new diagnosed disease or a symptom as part of the aging process (Mallet et al., 2007).

To prevent drug-drug interactions, interaction programs are usually used to warn of possible side effects, even before the drug is prescribed or dispensed. Unfortunately, the age of the patient and related other changed parameters are mostly not taken into account in those programs (Mallet et al., 2007). There are special critera that explicitly identify drugs that may

or may not be suitable for older adults. The Beers Critera created by the American Geriatrics Society (AGS) show potentially inappropriate drugs in older patients, which should be avoided in drug therapy. These criteria serve as guidelines for physicians and help them adapting their prescribing scheme to older people (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). In addition to the Beers Criteria, another list has been created that recommends alternative drugs in older patients. It serves as a useful tool for health professionals (Hanlon et al., 2015). Since there is no data on medical cannabis in older adults, it is still up to the physician to decide whether or not to prescribe a cannabis preparation for the patient.

1.4.4 Medical Cannabis Use in Older People

As already mentioned, especially older people are making increasing use of medicinal cannabis. Also, it is known that the adverse side effect and interaction potentials are significantly higher in older people than in younger ones. However, it is not clear yet what effect medicinal cannabis has on older adults.

Abuhasira et al. comes to different conclusions in two of his studies. While one study shows that medicinal cannabis is safe and effective in older people (Abuhasira et al., 2018), another study points out that there is too little evidence on the efficacy and safety of medical cannabis, especially when it comes to use in older adults. A benefit-risk assessment must therefore be made for each patient individually. In addition, patients undergoing medical cannabis therapy must be monitored continuously (Abuhasira et al., 2019).

1.5 Significance and Aim of Diploma Thesis

This study will provide one of the largest assessments of real-world cannabis-related adverse events and interactions based on FAERS. The FDA Adverse Event Reporting System has never been used for cannabis focused research yet, as far as we know. It will provide greater insight into possible drug-drug interactions with medical cannabis and will be informative for physicians and patients decision-making regarding possible risks and benefits of cannabis-based therapy. Data on recreational use cannot simply be extrapolated because not only the type of application but also the dosage and composition differ from that of medicinal cannabis (Karst, 2018). Due to the legalization of cannabis in many countries worldwide, this research results are of great relevance in an international context.

2 Methods

Disclaimer: Since the focus of this research project is extracting, cleaning, and analyzing data, a lot of different tables and new datasets have been created. These tables would exceed hundreds of pages, so only the most important tables have been inserted. Not mentioned tables, which are marked with ˣ, have been explained in detail, but can also be requested.

2.1 Data-Extraction Method

One of the first steps of this research project has been the data extraction of case reports, that deal with medicinal and recreational cannabis use. The database that has been used is called FAERS (FDA Adverse Event Reporting System) dashboard (U.S. Food and Drug Administration, 2019).

2.1.1 FDA Adverse Event Reporting System

2.1.1.1 Available Information in FAERS

The FAERS database provides various information about a reported case, like 'Case ID', 'Suspect Product Names', 'Suspect Product Active Ingredients', 'Reason for Use', 'Reactions', 'Serious', 'Outcomes', 'Sex', 'Event Date', 'Latest FDA Received Date', 'Case Priority', 'Patient Age', 'Patient Weight', 'Sender', 'Reporter Type', 'Report Source', 'Concomitant Product Names', 'Latest Manufacturer Received Date', 'Initial FDA Received Date', 'Country where event occurred', 'Reported to Manufacturer?', 'Manufacturer Control Number', 'Literature Reference', 'Compounded Flag'.

Additional information like dosage of medication or drug application form is available in the free-text case narrative, which can be requested by a Freedom of Information Act (FOIA) (U.S. Food and Drug Administration, 2020b). It needs to be anticipated that for various reasons a FOIA has not been requested, as it was planned originally. First, it was initially not clear which case reports should ultimately be analyzed in detail. It takes a long time before the request goes through until the narrative is finally available. That would have exceeded the time frame of the diploma thesis. Second, the pandemic would have made this a lot more complicated. After consultation with the advisor Dr. Brown, it has been decided to not request the case narrative. The focus remained on the publicly accessible FAERS database, although the case narrative would have made it a lot easier to make assumptions about the causality of an adverse event.

Since the information on FAERS is publicly available and has never been used for the extraction and analysis of medicinal cannabis case reports, it became the source of interest for this research project.

2.1.1.2 MedDRA Terms

To ensure a better comparison in between the reported cases, the adverse reactions of FAERS are categorized by the Medical Dictionary for Regulatory Activities (MedDRA) terms. The MedDRA terms are classified in a hierarchical order, including Lowest Level Terms (LLT), Preferred Terms (PT), High Level Terms (HLT), High Level Group Terms (HLGT) and System Organ Classes (SOC). LLT terminology consist of over 70,000 descriptors of adverse events, which decrease across the hierarchy of terms to just 27 SOC terms (Medical Dictionary for Regulatory Activities, 2020). MedDRA preferred terms (PT) are the ones that are mentioned in FAERS and that play a big role in the analysis of FAERS case reports.

2.1.2 Search Strategy

On the FAERS public dashboard it is possible to search for case reports either by drugs or by adverse events. All case reports where cannabis products are mentioned have been extracted, no matter what age or if it has been used medically or recreationally. Search terms or product names that have been used for the extractions are the following: 'Cannabidiol/Cannabis Sativa Seed Oil', 'Cannabidiol/Device/Herbals', 'Cannabidiol/Herbals/Menthol', 'Cannabidiol/ Herbals', 'Cannabidiol', 'Cannabinol', 'Cannabis Sativa Seed Extract', 'Cannabis Sativa Seed Oil/Device/Herbals', 'Cannabis Sativa Seed Oil', 'Cannabis Sativa Seed', 'Hemp', '11-Hydroxy-delta-9-tetrahydrocannabinol', '11-Nor-9-carboxy-delta-9-tetrahydrocannabinol', 'Cannabinoid, Synthetic (Nos)', 'Delta-8-Tetrahydrocannabinol', 'Delta-8-tetrahydrocannabinol/ Device/Herbals/Nicotine', 'Delta-8-tetrahydrocannabinol/Device/ Herbals', 'Delta-8-tetrahydrocannabinol/Herbals', 'Delta-9-tetrahydrocannabinolic Acid', 'Dronabinol', 'Nabilone', 'Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/Herbals', 'Cannabidiol/Delta-8-Tetrahydrocannabinol', 'Cannabis Sativa Flowering Top', 'Cannabis Sativa Subsp. Indica Top', 'Cannabis Sativa Subsp. Indica Top/Device', 'Cannabis Sativa Whole' and 'Nabiximols'.

At the end of the searching process, all case reports have been exported to Microsoft Excel.

2.2 Data-Processing Method

2.2.1 Sorting of FAERS in EXCEL

The following tables did not need any more information than the ones available on FAERS. Data has just been sorted and structured in a different way comparing to the original FAERS tables.

2.2.1.1 Table of Drugs [x]

After performing some Excel operations, removing duplicates, and getting rid of some salts and brand names, a list was created that contains all the drugs mentioned in the columns 'Suspect Product Active Ingredients' and 'Concomitant Product Names'. This 'Table of Drugs' shows the drugs that are often taken together with cannabis preparations, regardless of whether the drug-combination or cannabis itself play a role in the development of side effects. The table also shows if the drug was taken in a single-drug or multi-drug formulation. All in all, the table contains 593 drugs (without drug combinations).

2.2.1.2 Table of Cannabis Products

In this table every mentioned cannabis product has been divided into either 'THC'-product, 'CBD'-product or into a product that contains 'both' cannabinoids. The classification was made according to the main ingredients of the product itself. If neither THC nor CBD were included, it has been assigned to the group that more closely resembles the properties of CBD or THC. Sometimes the cannabis product contains THC and CBD with an unclear or similar proportion. Then the product was assigned to the group 'both'.

Table 5. Classification of Cannabis Products.

Cannabis Product	Description	Cannabis Group
Cannabidiol/Cannabis Sativa Seed Oil	Cannabis Sativa Seed Oil contains neither THC nor CBD (only traces of CBD) (Murray & Carter, 2020)	CBD
Cannabidiol/Device/Herbals		CBD
Cannabidiol/Herbals/Menthol		CBD
Cannabidiol/Herbals		CBD
Cannabidiol		CBD
Cannabis Sativa Seed Extract	in hemp seed no THC, it may contain THC because of contamination in harvesting process (Andre et al., 2016; Murray & Carter, 2020; Yang et al., 2017)	CBD
Cannabis Sativa Seed Oil/Device/Herbals	in hemp seed no THC, it may contain THC because of contamination in harvesting process (Andre et al., 2016; Murray & Carter, 2020; Yang et al., 2017)	CBD

Cannabis Sativa Seed Oil	in hemp seed no THC, it may contain THC because of contamination in harvesting process (Andre et al., 2016; Murray & Carter, 2020; Yang et al., 2017)	CBD
Cannabis Sativa Seed	in hemp seed no THC, it may contain THC because of contamination in harvesting process (Andre et al., 2016; Murray & Carter, 2020; Yang et al., 2017)	CBD
Hemp	Cannabis sativa with THC concentrations greater than 0.3%, ~5% CBD (Hilderbrand, 2018)	CBD
11-Hydroxy-delta-9-tetrahydrocannabinol	major metabolite of Delta-9-tetrahydrocannabinol (National Library of Medicine, 2020)	THC
11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	metabolite of Delta-9-tetrahydrocannabinol (National Library of Medicine, 2020)	THC
Cannabinol	metabolite of THC (National Library of Medicine, 2020)	THC
Cannabinoid, Synthetic (Nos)	act on same receptors as THC (Centers for Disease Control and Prevention, 2017)	THC
Delta-8-Tetrahydrocannabinol	delta-8-THC is an analogue of delta-9-THC with lower psychotropic potency (National Library of Medicine, 2020)	THC
Delta-8-tetrahydrocannabinol/Device/Herbals / Nicotine	delta-8-THC is an analogue of delta-9-THC with lower psychotropic potency (National Library of Medicine, 2020)	THC
Delta-8-tetrahydrocannabinol/Device/Herbals	delta-8-THC is an analogue of delta-9-THC with lower psychotropic potency (National Library of Medicine, 2020)	THC
Delta-8-tetrahydrocannabinol/Herbals	delta-8-THC is an analogue of delta-9-THC with lower psychotropic potency (National Library of Medicine, 2020)	THC
Delta-9-tetrahydrocannabinolic Acid	bio-synthetical precursor of Delta-9-tetrahydrocannabinol (National Library of Medicine, 2020)	THC
Dronabinol	synthetic form of Delta-9-tetrahydrocannabinol (Drugbank.com, 2020)	THC
Nabilone	synthetic form of Delta-9-tetrahydrocannabinol (Drugbank.com, 2020)	THC
Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/ Herbals	no percentage of amount (Caron, 2015; Grotenhermen & Göttsche, 2019)	Both
Cannabidiol/Delta-8-Tetrahydrocannabinol		Both
Cannabis Sativa Flowering Top	CBD (~<3%), THC (~15-25%) most of the time products have more THC, but sometimes also more CBD (Caron, 2015; Grotenhermen & Göttsche, 2019)	Both
Cannabis Sativa Subsp. Indica Top	no percentage of amount (most of the time more THC, sometimes more CBD) (Caron, 2015; Grotenhermen & Göttsche, 2019)	Both
Cannabis Sativa Subsp. Indica Top/Device	no percentage of amount (most of the time more THC, sometimes more CBD) (Caron, 2015; Grotenhermen & Göttsche, 2019)	Both
Cannabis Sativa Whole	no percentage of amount (most of the time more THC, sometimes more CBD) (Caron, 2015; Grotenhermen & Göttsche, 2019)	Both
Nabiximols		Both

Cannabis products mentioned in FAERS classified by CBD-group, THC-group or group with products containing both, CBD, and THC.

In table 5 the cannabis product was written in the first column, a description of some of the products in the second column and the assigned cannabis group in the last column. Cannabis products without any description can be easily assigned by its name.

2.2.1.3 Table of Reactions [x]

The 'Reaction' column from the original FAERS data shows all side effects that have been reported in the cannabis case reports. In this research the focus lies on four different categories of side effects, namely cardiovascular effects, neuropsychiatric effects, infectious effects, and sedative effects. These four outcomes play an important role in the outcomes of Cannabinoids, especially THC (Brown, 2020). If possible, reactions have been assigned to one or more reaction categories. Sometimes a side effect could not be classified, though (e.g. taste disorder, renal injury, colon cancer). Examples of the defined side effect classes are given in table 6.

Table 6. Classification of Reactions.

Side Effect Category	Examples
Cardiovascular effects	Acute cardiac event, angina pectoris, arrhythmia, blood pressure increased, cardiotoxicity, embolism, hemorrhagic stroke, hypertension, oedema
Neuropsychiatric effects	Abnormal behavior, acute psychosis, affective disorder, anxiety, bipolar disorder, completed suicide, confusional state, dementia, depression, dizziness, hallucination, mania, mental disorder
Infectious effects	Arthritis, bacteremia, bronchitis, Escherichia infection, gastritis, hepatitis, herpes zoster, infection, influenza, sepsis, joint swelling, pneumonia, viral infection
Sedative effects	Asthenia, hypersomnia, lethargy, loss of consciousness, sedation, somnolence

Some examples of reactions mentioned in FAERS sorted by four different side effect categories.

To assure the right classification of side effects to the afore-mentioned categories Lea Gnatzy, another pharmacy student from the University of Erlangen and research intern at the UF as well, supported with this research step. Overall, 973 side effects have been mentioned in cannabis case reports.

2.2.1.4 Tables of Case Reports with Various Diseases

The column 'Reason for Use' in the original FAERS database often gives information about patients' diseases or symptoms. The aim was to establish a correlation between cannabis use and a certain disease to identify possible drug-disease interactions.

In the first step, the focus was on case reports in which the individual had age-relevant and age-specific diseases. The diseases that have been taking a closer look at were Parkinson's disease, Alzheimer's disease, diabetes mellitus, arthritis, osteoporosis, chronic obstructive pulmonary disease, and liver diseases. Unfortunately, the information about 'Reason for Use' was often missing. That is why it has been decided to also look at the medications each patient takes. In the second step, the goal was to assume the individuum's disease just by looking at the medication list. Table 7 shows some drugs, that are very likely to indicate the disease. Sometimes it is not possible to infer the disease just by looking at the medication list, since a few drugs are approved for a broader variety of indications (table 8).

Table 7. Medications Indicating Diseases.

DISEASE	DRUGS
Parkinson's Disease	Levodopa/Carbidopa
Alzheimer's Disease	Rivastigmine
Diabetes II	Metformin
Osteoporosis	Alendronate, Ca
COPD	Spiolto

Some examples of specific drugs that are very likely to indicate the disease (DocCheck Community GmbH, 2020).

Table 8. Unspecific Medications Indicated for Various Diseases.

DISEASE	DRUGS	ALSO USED FOR
Arthritis	Methotrexate, abatacept	Psoriasis, Crohn's disease, ulcerative colitis
Liver Disease (e.g. hepatitis C)	Sofosbuvir	HIV

Some examples of unspecific drugs that are unlikely to indicate the disease (DocCheck Community GmbH, 2020).

The number of received case reports for each disease is very low and does not correspond to the actual prevalence in the population (Orphadata Report Series, 2020). Moreover, there are a lot of duplicates, e.g. from all the 22 cases with Parkinson's Diseases, 18 people have the same gender, age, similar drugs, reactions, etc. The reason for this is often multiple people (manufacturers, consumers, healthcare providers), who report the exact same case similar but still a bit different. Once cases are suspected as duplicates, they cannot simply be deleted because there is no evidence that they indeed are duplicates. Duplicates are one of the main problems of FAERS, partly because they do not make it possible to make statements about frequencies or prevalences.

2.2.1.5 Tables of Case Reports with Prescribed Cannabis Products [x]

In FAERS there are thousands of case reports that contain cannabis products, either for medicinal or recreational use. Important for this thesis are case reports, where cannabis was used medicinally from older adults. Case reports, that explicitly mention a medicinal cannabis product (Canemes, Cesamet, Epidiolex, Marinol, Syndros, Sativex) or, if no brand-name is given, the drug itself (nabilone, dronabinol, nabiximols), were extracted. These prescribed cannabis products have already been explained in detail in chapter 1.2.1. To compare the side effects in between different age groups, three tables have been created, one for people over 50 years of age, one for people under 50 years of age and one for people with no defined age. Very often age is missing in the case reports, which is why cases with 'undefined age' remain interesting.

2.2.2 Creating New Tables

Following tables needed more information than the information available on FAERS. Data has been extracted from various sources, which are mentioned below.

2.2.2.1 Pharmacokinetic Interactions Table

Major goal of this table was to find out possible pharmacokinetic interactions between cannabis ingredients and other drugs that might later be helpful to draw conclusions about the origin of side effects.

First, it was necessary to find out which enzymes and transporters are involved in the metabolism and transport of cannabinoids. The focus lied on three cannabis products, THC, CBD and nabiximols. THC and CBD are considered as the main pharmacologically active ingredients of cannabis, which is why they were picked as cannabinoids of interest. Nabiximols was picked as well, since it is a combination of both, THC and CBD, which is known to influence each other's effect (Solowij et al., 2019). Even if a pharmacokinetic interaction between the two substances can probably be ruled out (Karschner et al., 2011), the combination is nevertheless considered separately. Enzymes and transport systems that are involved in the metabolism of these cannabinoids were extracted from various papers described in chapter 1.1.3 and 'www.drugbank.ca' (Drugbank.com, 2020). Although the interactions slightly differ in between these sources, every interaction has been included. For example, in DrugBank it is written that CBD is a substrate of CYP2C19, whereas Qian, Gurley and Markowitz (Qian,

Gurley, & Markowitz, 2019) claim that CBD is an inhibitor of CYP2C19. Both pieces of information were collected in the 'Pharmacokinetic Interactions Table'.

In a further step each drug, which was mentioned in the FAERS reports, has been looked up on www.drugbank.com (Drugbank.com, 2020) and www.uptodate.com (UpToDate, Inc. and/or its affiliates, 2020) to find out whether those drugs interact with the same targets as the cannabinoids of interest. As soon as there was an interaction, it was also noted if the drug acts as substrate, inhibitor, or inductor (figure 1).

However, one must keep in mind that if no interaction is known, that does not necessarily mean that there is indeed no interaction in vivo.

A	B	C	D	E	F	G	H	I	J
Drugs	**CYP3A4**	**CYP3A5**	**CYP3A7**	**CYP3A**	**CYP2D6**	**CYP2C9**	**CYP2C19**	**CYP2A6**	**CYP2B6**
Cannabidiol	1(s,inh)	1(s,inh)	1(inh)	1(inh)	1(s,inh)	1(s,inh)	1(s,inh)	1(inh)	1(inh)
Delta-9-tetrahydrocannabinol (Dronabinol)	1(s,inh)	1(inh)	1(inh)	1(inh)	1(inh)	1(s,ind)	1(inh)	1(inh)	1(inh)
Nabiximols (CBD+THC)	1(s,inh)	1(s)	1(inh)	0	1(s,inh)	1(s)	1(s,inh)		
Abatacept									
Acetaminophen	1(s, ind)				1(s)			1(s)	
Acetylcysteine									
Acyclovir									
Adalimumab									
Alendronic Acid									
Alfuzosin	1(s)								
Alimemazine									
Alizapride									
Allopurinol									
Alprazolam	1(s)	1(s)	1(s)			1(s)			
Amantadine									
Aminosalicylic Acid									
Amiodarone	1(s, inh)				1(s, inh)	1(s, inh)	1(s, inh)	1(inh)	
Amisulpride									
Amitriptyline	1(s)	1(s)			1(s)	1(s)	1(s, inh)		1(s)
Amlodipine	1(s)	1(s, inh)			1(inh)				1(s, inh)
Amoxapine					1(s, inh)				
Amoxicillin									
Amphetamine					1(s)			1(inh)	
Ampicillin									
Anakinra									
Apixaban	1(s)	1(s)				1(s)	1(s)		
Apremilast	1(s)							1(s)	
Aprepitant	1(s, ind, inh)					1(ind, inh)	1(s, inh)		
Aripiprazole	1(s)	1(s)	1(s)		1(s)				
Armodafinil	1(ind)	1(ind)				1(inh)	1(inh)		1(ind)
Arnica Montana Flower *****									
Ascorbic Acid									
Aspirin						1(s)	1(ind)		
Atenolol					1(s)				
Atorvastatin	1(s)	1(s)	1(s)		1(inh)	1(inh)	1(inh)		1(ind)
Atropine									
Avelumab									
Azithromycin	1(s, inh)								

Figure 1. Excerpt of 'Pharmacokinetic Interactions Table'. *Small selection of table showing pharmacokinetic targets of all drugs in 'Table of Drugs'. 1 = interactions; s = substrate; ind = inductor; inh = inhibitor*

It is also interesting to know whether cannabis acts as a victim or a perpetrator. If the cannabis ingredient is an inhibitor/inductor and the additional drug A is a substrate of a specific enzyme, the cannabis ingredient acts as perpetrator and drug A as victim, and vice versa. This is because the inhibitor or inductor either inhibits or stimulates the metabolism of the substrate by interacting with the enzyme. If both the cannabis ingredient and drug A are substrates, a possible indirect interaction could take place because the substances may bind to the same

binding site of the enzyme and thus displace the other substance from the binding site, which would affect its metabolism. If both substances are inhibitors or inducers, they could act either as victims or perpetrators. Table 9 gives an overview of when the cannabis ingredient acts as victim or perpetrator. Figure 2 shows the relationship and interactions between enzyme, its victim, and its perpetrator. The created 'Pharmacokinetic Interactions Table' can be found in the appendix (table 33).

Table 9. Explanation of when Cannabis is Considered as Victim or as Perpetrator.

Enzym x (for example CYP3A4)	D (s)	D (inh/ind)	D (s, inh/ind)
C (s)	v*	v	V
C (inh/ind)	p	v*, p*	v*, p
C (s, inh/ind)	v*, p	v, p*	v, p

*D= Drug; s= substrate; inh/ind= inhibitor/inductor; v= cannabis as victim; p= cannabis as perpetrator; *= possible interaction; v*= substrate might displace other substrate in active site of enzyme; p*= inhibitor/inductor might also have an interaction with another inhibitor/inductor*

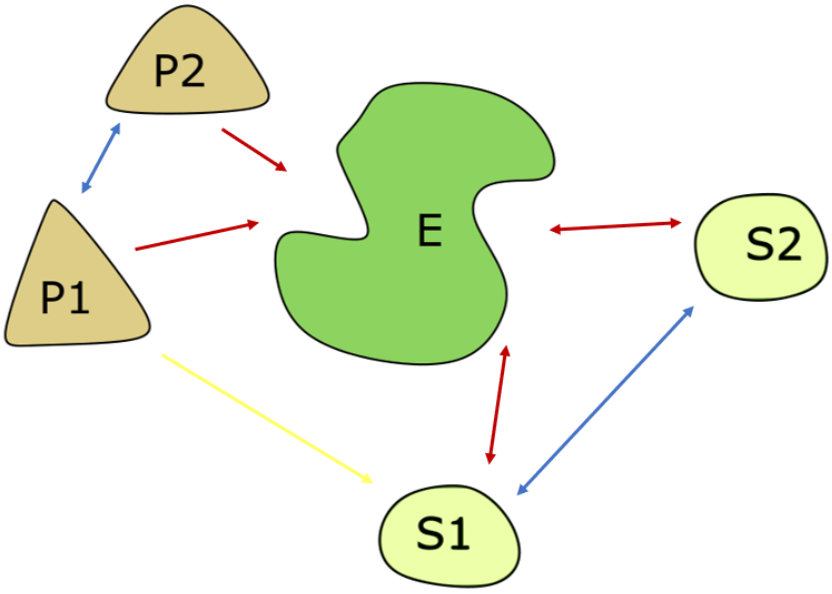


Figure 2. Graphical Representation of the Interaction of Enzyme, Perpetrator and Victim.
P1, P2 = Perpetrator (inductor, inhibitor); V1, V2 = Victim (substrate); red arrow = Interaction; blue arrow = possible interaction; yellow arrow = indirect interaction

2.2.2.2 Pharmacodynamic Interactions Table

The 'Pharmacodynamic Interactions Table' provides information about side effects of drugs, that are mentioned in the 'Table of Drugs'. If two drugs lead to the same side effect, a combination can produce a synergistic pharmacodynamic effect. When talking about pharmacodynamic interactions, it is of course also important to investigate which drugs compete for the same targets as CBD or THC do. Those targets are described in chapter 1.1.1.

Nevertheless, pharmacodynamic interactions that have been examined do not refer to the interactions of drugs on a certain receptor, but rather to the synergistic side effects in clearly defined side effect classes. The focus lied on reaction classes, that were previously defined, namely 'Cardiovascular Effects', 'Neuropsychiatric Effects', 'Infectious Effects' and 'Sedative Effects'. The frequency of side effects was expressed in the following way. '0' means the frequency of the effect is less than 1%, '1' means that the side effect is common with a frequency in between 1 and 10% and '2' means that the side effect is very common, with a frequency greater or equal 10%. For example, if the frequency of a cardiovascular event was 11%, number '2' was written in the 'Cardiovascular Effect'-category. '1°' means, that a side effect is mentioned but there is no frequency known. Still the frequency is assumed to be between 1 and 10%. 'Clinical Pharmacology' (Elsevier, 2020) and 'UpToDate' (UpToDate, Inc. and/or its affiliates, 2020), to which the UFL provided access, served as a data source. Table 34 'Frequency of Pharmacodynamic Reactions' in the appendix shows all drugs together with its frequencies of side effects.

Theoretically, if two substances lead to the same or similar cardiovascular side effect, the effects of both drugs together might lead to synergistic pharmacodynamic interactions. This means the reactions are consequently worse when taken drugs leading to the same reactions in combination. Since synergistic pharmacodynamic interactions have not been measured experimentally for this thesis, a rule has been established that states when an interaction is considered as synergistic. In order to be able to speak of strong synergistic side effects within a reaction class it has been decided that the sum of the frequencies of the combined drugs must be at least '3' within one reaction class. Number '3' is set arbitrarily, to not include all drugs having the side effect regardless of its frequency (e.g. '1°', where no frequency is known). This would be the case if '2' has been chosen as the required minimal value. If, for example, CBD is combined with Abatacept, both drugs lead to their individual side effects. With Abatacept cardiovascular and neuropsychiatric side effects are common ('1'), infections even very common ('2'). CBD, on the other hand, has little effect on the cardiovascular system ('0'), whereas neuropsychiatric side effects are frequent ('1'), infections and sedation are very common ('2'). Since both drugs lead to a high chance of infections ('2') the likelihood of infections is significantly increased when taking both substances ('2' + '2' = '4' → ≥ '3' → strong synergistic pharmacodynamic interaction). Figure 3 shows an excerpt from the table in which the side effect frequencies of cannabis ingredients and various drugs were added.

In the ultimate synergistic 'Pharmacodynamic Interaction Table' [x], 'yes' is written for a minimum total of '3' and 'no' for a 'lower total than 3'. Figure 4 shows an excerpt of this table, which is relevant for later purposes.

		Cardiovascular Side Effects	Neuropsychiatric Diseases	Effect on Infections	Sedation
Abatacept	CBD	1	2	4	2
	THC	2	3	3	0
	Nabiximols	2	2	2	1
Acetaminophen	CBD	1	2	2	2
	THC	2	3	1	0
	Nabiximols	2	2	0	1
Acetylcysteine	CBD	0	1	2	2
	THC	1	2	1	0
	Nabiximols	1	1	0	1
Acyclovir	CBD	0	2	2	2
	THC	1	3	1	0
	Nabiximols	1	2	0	1
Adalimumab	CBD	1	2	4	2
	THC	2	3	3	0
	Nabiximols	2	2	2	1
Alendronic Acid	CBD	0	1	2	2
	THC	1	2	1	0
	Nabiximols	1	1	0	1
Alfuzosin	CBD	1	2	2	2
	THC	2	3	1	0
	Nabiximols	2	2	0	1
Alimemazine	CBD	1	1	2	2
	THC	2	2	1	0
	Nabiximols	2	1	0	1
Alizapride	CBD	1	1	2	2
	THC	2	2	1	0
	Nabiximols	2	1	0	1

Figure 3. Excerpt from the Table with Combined Pharmacodynamic Side Effects. *Small excerpt from the table that added up the frequencies of side effects of any drug together with one of the three investigated cannabis ingredients.*

	Cardiovascular Side Effects			Neuropsychiatric Diseases			Effect on Infections			Sedation		
	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols
Abatacept	no	no	no	no	yes	no	yes	yes	no	no	no	no
Acetaminophen	no	no	no	no	yes	no	no	no	no	no	no	no
Acetylcysteine	no	no	no	no	no	no	no	no	no	no	no	no
Acyclovir	no	no	no	no	yes	no	no	no	no	no	no	no
Adalimumab	no	no	no	no	yes	no	yes	yes	no	no	no	no
Alendronic Acid	no	no	no	no	no	no	no	no	no	no	no	no
Alfuzosin	no	no	no	no	yes	no	no	no	no	no	no	no
Alimemazine	no	no	no	no	no	no	no	no	no	no	no	no
Alizapride	no	no	no	no	no	no	no	no	no	no	no	no
Allopurinol	no	no	no	no	no	no	no	no	no	no	no	no
Alprazolam	no	no	no	yes	yes	yes	no	no	no	yes	no	yes
Amantadine	no	yes	yes	yes	yes	yes	no	no	no	no	no	no
Aminosalicylic Acid	no	no	no	no	no	no	no	no	no	no	no	no
Amiodarone	no	no	no	no	yes	no	yes	no	no	no	no	no
Amisulpride	no	no	no	yes	yes	yes	no	no	no	no	no	no
Amitriptyline	no	yes	yes	yes	yes	yes	no	no	no	yes	no	no
Amlodipine	no	no	no	no	yes	no	no	no	no	no	no	no
Amoxapine	no	no	no	yes	yes	yes	no	no	no	no	no	no
Amoxicillin	no	no	no	no	no	no	yes	no	no	no	no	no
Amphetamine	no	yes	yes	yes	yes	yes	yes	yes	no	no	no	no
Ampicillin	no	no	no	no	no	no	yes	no	no	no	no	no
Anakinra	no	no	no	no	no	no	yes	yes	no	no	no	no
Apixaban	no	no	no	no	no	no	no	no	no	no	no	no
Apremilast	no	no	no	no	yes	no	yes	yes	no	no	no	no
Aprepitant	no	no	no	no	yes	no	yes	no	no	no	no	no

Figure 4. Excerpt from 'Pharmacodynamic Interaction Table' [x]. *No = presumably no strong pharmacodynamic interaction with CBD/THC/nabiximols; yes = presumably pharmacodynamic interaction with CBD/THC/nabiximols; - = no information available about this drug on websites*

As already discovered in studies, a combination of CBD and THC is better tolerated by the human body, as CBD curbs the strong hallucinogenic effects of THC (Solowij et al., 2019). Possibly this is the reason why nabiximols, the combination of both substances, has fewer side effects than THC and CBD have when considered individually. However, it could also be because there is simply a lot less data available about nabiximols and its side effects.

2.2.2.3 Drug Interactions Table [x]

Interactions in between drugs have also been checked by interaction programs. Two have been used for this analysis, namely 'Wechselwirkungscheck' from www.doccheck.com (Dosing GmbH Heidelberg, 2020) and 'Drug Interactions Checker' from www.drugs.com (Drugs.com, 2020b). Soon it has been realized that the information differs within the websites and that 'Wechselwirkungscheck' shows far fewer interactions. Lea Gnatzy helped again by extracting interactions from those websites. A table with already known interactions between cannabis preparations (Cannabis sativa, CBD, dronabinol, nabilone) and drugs mentioned in the 'Table of Drugs' has been created. If the website provided more information about the strength or type of interaction, it also has been added to the table.

The 'Drug Interactions Table' (excerpt in figure 5) is intended to serve as a comparison with other study results. In the end, the aim was to find possible interactions that are not known yet in the interaction databases.

Drugs	Cannabis Sativa	CBD	Dronabinol	Nabilone	Details about Interaction
Abatacept	-	-	-	-	
Acetaminophen	-	moderate	-	-	CBD: liver problems
Acetylcysteine	-	-	-	-	
Acyclovir	-	-	-	-	
Adalimumab	-	-	-	-	
Alendronic Acid	-	-	-	-	
Alfuzosin	-	moderate	-	moderate	Nabilone & CBD: decreased blood pressure
Alimemazine	not found	not found	not found	not found	
Alizapride	-	-	-	-	
Allopurinol	-	-	-	-	
Alprazolam	moderate	moderate	moderate	moderate	All: dizziness, drowsiness, confusion
Amantadine	-	-	-	-	
Aminosalicylic Acid	-	moderate	-	-	CBD: liver problems
Amiodarone	-	moderate	-	-	CBD: liver problems
Amisulpride	-	-	-	-	
Amitriptyline	moderate	moderate	moderate	moderate	All: dizziness, drowsiness, confusion
Amlodipine	moderate	moderate	moderate	moderate	All: dizziness, drowsiness, confusion
Amoxapine	moderate	moderate	moderate	moderate	All except CBD: dizziness, drowsiness, confusion
Amoxicillin	-	-	-	-	
Amphetamine	-	-	-	-	
Ampicillin	-	-	-	-	

Figure 5. Excerpt from the Drug Interactions Table [x]. *This table shows all interactions that have been found on 'Wechselwirkungscheck or 'drug interactions checker' (Dosing GmbH Heidelberg, 2020; Drugs.com, 2020b).*

2.3 Statistical Method

2.3.1 Failed Statistical Approach

There are some calculations regarding disproportionality analysis, which serve to find trends in a database and thus detect a safety signal. Some common methods are for example the calculation of Proportional Reporting Ratio (PRR) or Reporting Odds Ratio (ROR), which are very similar to the odds ratios and risk ratios (Bate & Evans, 2009).

$$ROR = \frac{\frac{A}{C}}{\frac{B}{D}} \qquad PRR = \frac{\frac{A}{(A+B)}}{\frac{C}{(C+D)}}$$

Table 10. Contingency Table for Disproportionality Analysis.

	Reaction Y	
Drug X	yes	No
yes	A	B
no	C	D

This contingency table serves as the basis for calculating ROR and PRR (Bate & Evans, 2009).

A lower limit of 95% confidence interval is calculated as a standard for PRR and ROR. These metrics are useful for between-drugs analysis, a comparison of factors related to reports of drug X1 and factors related to reports of drug X2. ROR and PRR are both based on a 2x2 contingency table, looking alike table 10.

Limitations of FAERS data are besides no randomization of treatment groups, missing information and duplicates, the lack of a denominator, which is important to standardize the frequency of an event observed against the frequency of people receiving therapy (U.S. Food and Drug Administration, 2018). A solution is to use the entire FAERS database as denominator, which represents the number of non-event cases without exposure. Major goal is to find a trend in events occurring in the exposure group. Since this research has a focus on older people and asks the question, if age might have an influence on the outcome, it is interesting to look at the metrics in various age groups, in order to compare them with each other. Later, information on pharmacokinetic and pharmacodynamic interactions, which have been gathered before, would have served as an additional data source for evaluating the effects of interactions on the outcomes. In a study from Brown et al. (Brown et al., 2019)

researchers also worked with FAERS data as information source. They used similar statistical calculations for their analysis like in the afore-mentioned paper.

Unfortunately, this statistical approach did not work out as well with the research question of this thesis. In the extracted FAERS case reports there are more than 900 different reactions described, which are often similar but still not the same (e.g. 'Blood Pressure Decreased' and 'Blood Pressure Abnormal'). The intention was to summarize all reactions into bigger categories and add up their frequencies in order to find out the number of reports in each category. This approach did not work, because most of the case reports contain more than one reaction, e.g. 'depression' and 'depressive disorder'.

In the next step the focus was on eight different reactions (cardiovascular side effect: acute myocardial infarction, cardiotoxicity; neuropsychiatric side effect: cognitive disorder, psychotic disorder; infectious side effect: infection, pneumonia; sedative side effect: sedation, lethargy). ROR and PRR have been calculated, although the fact that FAERS contains many duplicates weakens the reliability of the calculated values. To compare side effects between <50 and >50 years old patients and side effects related to THC, CBD and nabiximols, ROR and PRR needed to be calculated for every single subgroup separately. This was impossible, because the case number of CBD- and nabiximols-cases with defined age was low, leading to not reliable statistical calculations. This is because the ratio of a low number of cases (e.g. 15) cannot be set in relation with a ratio of a high number of cases (e.g. 19,000,000), what needs to be done for calculating ROR and PRR.

Unlike other research groups did, no comparator drug was chosen. That was because the question of this research was to find out, which drugs might interact with THC/CBD/nabiximols and not if drug A makes more side effects/interactions than drug B.

2.4 Descriptive Method

2.4.1 General Calculations about FAERS

Before individual case reports have been analyzed, a few general calculations of the FAERS data were made to be able to put the cannabis reports in relation. The information and calculations collected relate to all case reports between 1968 and 2020 (as of May 21st, 2020). General numbers about the FAERS database, including information about report type, reporter region and report seriousness have been calculated.

2.4.2 Calculations about Cannabis Case Reports [x]

One table shows the number of cannabis case reports sorted by age (<50,> 50, not defined age) and by cannabis product. A similar table provides a good picture of the distribution among the different gender (male, female, not specified). A third table includes the number of case reports for each cannabis product, sorted by CBD/THC/nabiximols. Other data like the frequency of individual reactions, frequency of reactions sorted by reaction group, frequency of all mentioned drugs and number of drugs per report have also been calculated. Relevant and interesting calculations are mentioned in chapter 3. These calculations might serve as a basis to find out, if there is a trend or correlation in between age/gender, medically prescribed cannabis products and cannabis side effects.

2.4.2.1 Prescribed Cannabis Reports [x]

Due to the fact that the focus lies on medical cannabis use, case reports that contain medically approved cannabis products were extracted. Cases without prescribed cannabis products were not included and not assumed as medical use. If cases did not contain the brand name but the drug name, they were included as long as they contained nabilone, dronabinol and nabiximols, but not cannabidiol. This is because the first three drugs are normally prescribed and not available for recreational use, whereas the fourth drug, cannabidiol, is. In later chapters, data about medicinal cannabis can be compared to data about recreational cannabis.

2.4.2.2 Pharmacokinetic-Pharmacodynamic Correlation [x]

The previously created 'Pharmacokinetic Interactions Table' and 'Pharmacodynamic Interactions Table' serve as the basis for the 'Pharmacokinetic-Pharmacodynamic Correlation Table'. Both tables, which are based on data collected from the world wide web, were merged. Interactions that are less probable (*) were not taken into account and considered as no interaction. If no information about a specific drug was available on Drugbank (-), no interaction has been assumed as well. By merging those two tables it is possible to see whether the suspected pharmacokinetic interactions also correlate with pharmacodynamic interactions. Excel again served as working surface. Merging has been simplified by using various commands.

The result was a table with a lot of information for each individual drug. It shows the presumed pharmacokinetic interactions with CBD/THC/nabiximols, the strong pharmacodynamic synergistic interactions with CBD/THC/nabiximols and the correlation between pharmacokinetic and pharmacodynamic interactions together with other drugs. Correlation means that there might be a connection between the pharmacokinetic interaction and the synergistic interaction in between the cannabis ingredient and the additional drug taken. A possible correlation is assumed as soon as both interactions apply to a certain extent. At one glance, this table shows interactions, already known in literature, for each drug investigated in this work. This table is used for further trend analysis and evaluation of interactions in the next chapters. A separate table was created for each drug, which shows the interaction with cannabis ingredients. A total of 593 tables were created. As an example, the table for alprazolam is shown in figure 6.

11 Alprazolam		Cardiovascular Side Effects			Neuropsychiatric Diseases			Effect on Infections			Sedation		
		CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols
	Presumable PK-Interactions with	no	no	no	yes	yes	yes	no	no	no	yes	no	yes
	CBD	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	as Victim	0	0	0	0	0	0	0	0	0	0	0	0
	as Perpetrator	3	3	3	3	3	3	3	3	3	3	3	3
	THC	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	as Victim	0	0	0	0	0	0	0	0	0	0	0	0
	as Perpetrator	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
	Nabiximols	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	as Victim	1	1	1	1	1	1	1	1	1	1	1	1
	as Perpetrator	3	3	3	3	3	3	3	3	3	3	3	3
	PK-PD-Correlation	no	no	no	yes	yes	yes	no	no	no	yes	no	yes
	CBD as victim	-			-			-			-		
	CBD as perpetrator	-			inhibitor			-			inhibitor		
	THC as victim		-			-			-			-	
	THC as perpetrator		-			-			-			-	
	Nabiximols as victim			-			substrate			-			substrate
	Nabiximols as perpetrator			-			inhibitor			-			inhibitor

Figure 6. Pharmacokinetic-Pharmacodynamic Correlation Table. *Presumable correlation between pharmacodynamic and pharmacokinetic interaction on the example of alprazolam.*

2.4.2.3 List with Interesting Drugs

The ‘List with Interesting Drugs’ is intended to provide a summary of existing data from the literature and to make comparisons with one another possible. Aim is to find drugs which often lead to side effects in older people, when taken together with any cannabis product.

Information was not only extracted from papers, but also from interaction programs and previously created tables, which are based on data from Drugbank, UpToDate and Clinical Pharmacology. Frequencies that show how often drugs appear in the case reports are also listed. The primary interest for further analysis is drugs, which often lead to side effects in combination with cannabis preparations. If a drug is mentioned frequently, but the literature

does not contain any data about interactions, a closer examination of the drug could reveal unknown interactions to serve as a guideline for future studies.

In order to simplify the analysis, a table was created for each of the three cannabis ingredients (CBD, THC and nabiximols) showing all available information about interactions with reported drugs. Those tables can be found in a reduced form in the appendix (table 35,36,37). However, the Excel files, which are available on request, are much more informative. The columns in Excel give the following information. The first column (column A) lists all reported drugs. Columns B-D indicate how often these drugs are reported in combination with cannabis among people over 50 years of age (column B), under 50 years of age (column C) and at an undefined age (column D, especially relevant for CBD cases). Since the FAERS dashboard is a messy database with a lot of duplicates, the statistical analysis is not reliable enough. Nevertheless, the frequencies of the drugs mentioned were considered because despite duplicates there is a certain truth behind the frequencies. If a drug is highlighted in light red it indicates a drug frequency of over 1% in relation to all reported cases of the subgroup, dark red indicates a frequency of over 10%. Columns E and F, which have been hidden in the appendix but can be displayed when viewing the Excel file [x], served as an aid in the analysis of important drugs. Figure 7 shows an excerpt of hidden columns E and F. In column E, some drugs are highlighted in a specific color. Dark red means that this drug is reported significantly more often in people over 50 years than in younger people (e.g. ampicillin in THC case reports). All drugs marked in dark red are relevant and might serve as an indication of which medicinal substances interact with cannabis and should be investigated more closely in future studies. Light red means that there is no significant difference in the frequency of the reported drug between younger and older patients (e.g. amisulpride in THC case reports). The blue color shows that the combination of cannabis and the drug leads more frequently to reactions in younger people which, however, very likely correlates with a higher usage of the drug in younger patients. Even if these cannabis preparations have been prescribed medically, misuse cannot be ruled out. Especially when people, often young ones, consume other drugs that are addictive or trigger addictive behavior (e.g. heroine), it is obvious that cannabis is also misused. It is therefore difficult to say that younger patients have more frequent interactions with substances such as alprazolam, amphetamines, benzodiazepines, cocaine, etc. Presumably, the consumption is simply increased. The yellow color indicates that drugs are mainly used by older patients. Therefore, no statements can be made about the fact that

particularly older people suffer from more frequent interactions between the drug and cannabis (e.g. amantadine, carbidopa). Column G indicates whether there may be a correlation between pharmacokinetic and pharmacodynamic interactions, which has already been described in detail in chapter 3.3.3. The number showing correlation can be in between 0 and 4. A prerequisite for a correlation is first and foremost at least one pharmacokinetic interaction. Depending on how many synergistic pharmacodynamic interactions occur in the four different categories of side effects, the correlation number is then '1', '2', '3' or '4'. Column H shows whether there are already known interactions in literature, which have been found in studies, be it in-vitro or in-vivo investigations. Details about the interaction can be found in column I, which can be displayed in the Excel file [x]. Column J, a column that is hidden as well, indicates the source of the information from column H and I. Column K shows what results interaction programs come up with. In column L, also hidden, more details on the interaction that appears in interaction programs are described. Column M shows whether the drug is of interest to further analysis. Column N gives additional information on the combination of the drug together with cannabis and resulting interactions.

	A	B	C	D	E	F
1	**Drugs**	**# of reports ≥ 50 years**	**# of reports < 50 years**	**# of reports not defined age**		Column B-D
2	Abatacept	4	3	2		light red: over 1% frequency
3	Acetaminophen	22	113	21		dark red: over 10% frequency
4	Acetylcysteine	0	0	0		Column E
5	Acyclovir	8	6	8		relevant
6	Adalimumab	2	2	3		similar frequency in older and younger people
7	Alendronic Acid	0	0	1		more reported in younger patients
8	Alfuzosin	0	0	1		more prescribed for older patients
9	Alimemazine	0	12	0		
10	Alizapride	2	0	0		
11	Allopurinol	2	5	0		
12	Alprazolam	16	81	12		
13	Amantadine	22	0	8		
14	Aminosalicylic Acid	2	0	0		
15	Amiodarone	2	0	0		
16	Amisulpride	9	8	0		
17	Amitriptyline	43	25	26		
18	Amlodipine	15	2	2		
19	Amoxapine	1	0	0		
20	Amoxicillin	1	2	0		
21	Amphetamine	2	70	3		
22	Ampicillin	16	0	0		

Legend | CBD | THC | Nabiximols

Figure 7. Excerpt of 'List with Interesting Drugs'. *Hidden columns E and F are displayed in this screenshot.*

Creating this table was helpful to get an overview about already known information and to find drugs, that might be interesting for future studies.

Together with Dr. Brown, it has been decided to not only make a descriptive analysis of FAERS cases including cannabis, but also describe some individual case reports. The focus was on

case reports containing drugs, that have been considered as interesting. The exact search strategy of the individual case reports is described in the next chapter.

2.4.2.4 Search Strategy for Individual Case Reports

Case reports that contained people with 50 years and older suffering from serious outcomes have been selected. Also, cannabis needed to be considered as being the cause of the outcome. Cannabis or its ingredients were always reported as suspected products, either alone or together with a concomitant drug. It has been tried to not pick case reports with a high number of suspected drugs, since this makes it even harder to assess which drug is responsible for all mentioned side effects. In the next step, reports that contained previously defined interesting drugs have been examined more closely. It was also important to select cases where not many concomitant drugs were listed (maximum 6). The less drugs are taken, the higher the probability that cannabis itself is the perpetrator and in charge of the side effect or interaction. Case reports where the outcome is very likely to be related to the diagnosed disease were excluded. The last step was to find two individual cases for each defined reaction category, ideally with two different genders. In addition, case reports with a lot of comorbidities (many different terms in 'Reason for Use' column) were neglected. The more factors (drugs, co-diseases) play a role in the case, the more difficult it is to infer side effects or interactions of cannabis.

12 specific cases from six different categories where cannabis is used medicinally have been described. Prescribing information was used for detailed analysis. In addition, each individual case was examined in the interaction program. Not all the information of the case reports is necessary for further analysis. Some columns from the original database have not been taken into account, like 'Suspect Product Names', 'Serious', 'Outcomes', 'Event Date', 'Latest FDA Received Date', 'Sender', 'Case Priority', 'Report Source', 'Reporter Type', 'Latest Manufacturer Received Date', 'Initial FDA Received Date', 'Country where event occurred', 'Reported to Manufacturer?' , 'Manufacturer Control Number', 'Literature Reference' and 'Compounded Flag'.

3 Results

3.1 Overall Picture

When looking at the entire FAERS database, which has been documented since 1968, 19,751,319 case reports are listed (according to May 21st, 2020). 55% of them are to be taken seriously, including death as an outcome, death itself makes up almost 10%. Reporting is shared equally by consumers (47.38%) and healthcare professionals (47.81%). About 70% of the reports are from the U.S., and about 30% of the case reports are from abroad. Those numbers are shown in table 11.

Table 11. Case Reports in FAERS 1968-2020.

		# of all Cases	% of all Cases
General Information	All Reports	**19,751,319**	100.00%
	Serious (including deaths)	10,989,688	55.64%
	Deaths	1,910,212	9.67%
Reports by Report Type	Expedited	10,530,464	53.32%
	Non-Expedited	8,239,138	41.71%
	Direct	980,845	4.97%
	BSR	863	0.00%
Reports by Reporter	Consumer	**9,358,360**	47.38%
	Healthcare Professional	**9,442,457**	47.81%
	Non Specified	941,973	4.77%
	Other	8,520	0.04%
Report by Reporter Region	USA	13,823,599	69.99%
	Other Countries	5,885,803	29.80%
	Non Specified	41,908	0.21%
Report by Report Seriousness	Serious	**10,989,688**	55.64%
	Deaths	1,919,212	9.72%
	Non-Serious	6,851,410	34.69%

Overview about all reported cases from 1968-2020, according to May 21st, 2020. Denominator is 19.751.319, the sum of all case reports. # = number; % = percent

Table 12. General Calculations About Cannabis Case Reports.

Prevalence Reaction with Cannabis Product (Cannabis Case Reports ÷ All Reports * 100)	0.05%
Prevalence Serious Reaction with Cannabis Product (Cannabis Case Reports (serious) ÷ All Reports (serious) * 100)	0.07%
Prevalence Death with Cannabis Product (Cannabis Case Reports (death) ÷ All Reports (death)*100)	0.13%

Prevalence of cannabis case reports based on all reports.

All in all, 10,687 case reports could be found after reducing duplicates. Duplicates can only be deleted if all columns of a case report are identical to those of another case report. However, some duplicates cannot be recognized as there are small differences due to different reporters

for the same case. From all FAERS case reports, around 0.05% include cannabis products. 0.07% of all serious case reports have to do with cannabis products, 0.13% of all case reports with the outcome death deal with cannabis products (table 12).

Table 13 shows the distribution of all cannabis case reports compared to the individual cannabis products. Almost 40% of reported cannabis related case reports contain cannabidiol (4,227 case reports), 38% Cannabis sativa subsp. indica top (4,039 case reports) and around 13% dronabinol (1,342 case reports). The fourth most frequently reported cases are those with Cannabis sativa flowering top (389 case reports). In place five there is nabilone (319 case reports).

Table 13. Distribution of Cannabis Products.

	Reports of Product X ÷ All Cannabis Reports *100
11-Hydroxy-delta-9-tetrahydrocannabinol	0.06%
11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	0.21%
Cannabidiol/Cannabis Sativa Seed Oil	0.25%
Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/Herbals	0.09%
Cannabidiol/Delta-8-Tetrahydrocannabinol	0.15%
Cannabidiol/Device/Herbals	0.16%
Cannabidiol/Herbals/Menthol	0.02%
Cannabidiol/Herbals	0.97%
Cannabidiol	**39.55%**
Cannabinoid, Synthetic (Nos)	0.18%
Cannabinol	0.24%
Cannabis Sativa Flowering Top	3.64%
Cannabis Sativa Seed Extract	0.04%
Cannabis Sativa Seed Oil/Device/Herbals	0.01%
Cannabis Sativa Seed Oil	0.30%
Cannabis Sativa Seed	0.05%
Cannabis Sativa Subsp. Indica Top/Device	0.21%
Cannabis Sativa Subsp. Indica Top	**37.79%**
Cannabis Sativa Whole	0.02%
Delta-8-tetrahydrocannabinol/Device/Herbals/Nicotine	0.04%
Delta-8-tetrahydrocannabinol/Device/Herbals	0.62%
Delta-8-tetrahydrocannabinol/Herbals	0.05%
Delta-8-tetrahydrocannabinol	0.41%
Delta-9-tetrahydrocannabinolic Acid	0.11%
Dronabinol	**12.56%**
Hemp	0.29%
Nabilone	2.98%
Nabiximols	0.36%

Percentage of case reports containing any cannabis product compared to all cannabis case reports in FAERS.

The following chapters focus on the question if there is a trend in cannabis use regarding age, gender, different cannabis products and medicinally prescribed cannabis.

3.1.1 Age-Specific Analysis of Case Reports Containing Cannabis Products

When looking at all extracted cannabis case reports, around 10% were people with 50 years of age or older. Around 39% were people under 50 years, 51% of case reports did not contain any specified age (table 14).Table 15 shows the age distribution of people who have taken various cannabis preparations and where a report has been made due to side effects, be it from cannabis or not.

Table 14. Age-Specific Calculations About Cannabis Case Reports.

Cannabis Case Reports when ≥ 50 years on all Cannabis Case Reports (Age ≥50 all Cannabis Case Reports ÷ All Cannabis Case Reports * 100)	10.03%
Cannabis Case Reports when < 50 years on all Cannabis Case Reports (Age <50 all Cannabis Case Reports ÷ All Cannabis Case Reports * 100)	39.17%
Cannabis Case Reports when not specified age on all Cannabis Case Reports (not specified age all Cannabis Case Reports ÷ All Cannabis Case Reports * 100)	50.81%

Prevalence of age-specific reports based on all reports.

Table 15. Cannabis Case Reports Sorted by Age.

	All Ages	Age ≥ 50	Age < 50	Age not specified
11-Hydroxy-delta-9-tetrahydrocannabinol	6	0	6	0
11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	22	4	15	3
Cannabidiol/Cannabis Sativa Seed Oil	27	10	12	5
Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/Herbals	10	0	9	1
Cannabidiol/Delta-8-Tetrahydrocannabinol	16	2	12	2
Cannabidiol/Device/Herbals	17	3	14	0
Cannabidiol/Herbals/Menthol	2	0	2	0
Cannabidiol/Herbals	104	31	47	26
Cannabidiol	4,227	31	217	3,979
Cannabinoid, Synthetic (Nos)	19	1	18	0
Cannabinol	26	1	19	6
Cannabis Sativa Flowering Top	389	59	280	50
Cannabis Sativa Seed Extract	4	0	4	0
Cannabis Sativa Seed Oil/Device/Herbals	1	0	1	0
Cannabis Sativa Seed Oil	32	8	14	10
Cannabis Sativa Seed	5	0	5	0
Cannabis Sativa Subsp. Indica Top/Device	22	3	17	2
Cannabis Sativa Subsp. Indica Top	4,039	420	2,727	892
Cannabis Sativa Whole	2	0	1	1
Delta-8-tetrahydrocannabinol/Device/Herbals/Nicotine	4	1	2	1
Delta-8-tetrahydrocannabinol/Device/Herbals	66	9	47	10
Delta-8-tetrahydrocannabinol/Herbals	5	1	2	2
Delta-8-tetrahydrocannabinol	44	3	28	13
Delta-9-tetrahydrocannabinolic Acid	12	0	12	0
Dronabinol	1,342	320	670	352
Hemp	31	4	17	10
Nabilone	319	158	84	77
Nabiximols	39	15	15	9
∑ (with duplicates)	10,832	1,084	4,297	5,451
Cannabis Case Reports (without duplicates)	**10,687**	**1,072**	4,186	5,430

Overview about the number of cannabis case reports sorted by age and cannabis product.

There is a similar trend in frequently reported cannabis products among those people over 50 years compared to all other age groups together (table 13). The front runner among the frequently reported products are again Cannabis sativa subsp. indica top, dronabinol, nabilone, Cannabis sativa flowering top and cannabidiol. A similar distribution is also observed among those under 50 years of age, with the number of case reports being around four times as high as the number of those over 50 years of age. This is probably less due to a reduced susceptibility to side effects but more to a reduced consumption of cannabis preparations in the older generation. One cannabis product, namely nabilone, is worth mentioning since there are more reports related to nabilone in the older generation than in the younger one. When looking at case reports containing nabiximols, side effects affect equally those under and over 50 years of age. One reason for this could be that old people simply take these drugs more often than young people.

A closer look at the last column with the non-defined age groups reveals a major deficit in the database. 3,979 out of the 4,227 (94%) case reports of cannabidiol do not indicate any age. This makes it very difficult to make correct statements about age-specific or age-dependent side effects. Even with Cannabis sativa subsp. indica top (892 out of 4,039 cases, around 22%) and dronabinol (352 out of 1,342 cases, around 26%) a certain proportion of reports did not contain any information about age. Most of the time, outcomes of case reports that contain cannabis products are serious except of case reports containing CBD. Only a quarter of the reported CBD cases have serious side effects.

3.1.2 Gender-Specific Analysis of Case Reports Containing Cannabis Products

On closer examination of the gender distribution, the following things became apparent. Male people were affected in 35% of all case reports, whereas women only in 22%. 43% of the cannabis related case reports did not contain any information about the gender (table 16).

Table 16. Gender-Specific Calculations About Cannabis Case Reports.

Cannabis Case Reports when male divided by all Cannabis Case Reports (Cannabis Case Reports male ÷ All Cannabis Case Reports * 100)	35.29%
Cannabis Case Reports when female divided by Cannabis Case Reports (Cannabis Case Reports female ÷ All Cannabis Case Reports * 100)	21.95%
Cannabis Case Reports when gender not specified divided by Cannabis Case Reports (all Cannabis Case Reports not specified gender ÷ All Cannabis Case Reports * 100)	42.76%

Prevalence of gender-specific reports based on all reports.

Almost every cannabis product mentioned in FAERS is reported more frequently in men than women (table 17). 259 men and 109 women appear in reports with Cannabis sativa flowering top. The distribution for Cannabis sativa subsp. indica top is 2,369 men vs. 1,277 women, whereby a large proportion of cases with Cannabis sativa subsp. indica top did not specify a defined gender (393 cases). 750 males and 487 females are mentioned in dronabinol case reports. The gender distribution is slightly different with 2 preparations. Side effects associated with nabilone and nabiximols are more commonly reported in women. The distribution of reported cases with nabilone is 54% women and 30% men, the one with nabiximols 59% women and 33% men. Only in the case of cannabidiol a similar proportion of women (131 cases) and men (147 cases) is found, although 93% of all reported cannabidiol cases provide no information about gender.

Table 17. Gender-Specific Calculations About Cannabis Case Reports.

	Both Gender	Male	Female	Not Specified
11-Hydroxy-delta-9-tetrahydrocannabinol	6	6	0	0
11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	22	13	6	3
Cannabidiol/Cannabis Sativa Seed Oil	27	14	11	2
Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/Herbals	10	6	4	0
Cannabidiol/Delta-8-Tetrahydrocannabinol	16	8	6	2
Cannabidiol/Device/Herbals	17	9	8	0
Cannabidiol/Herbals/Menthol	2	0	2	0
Cannabidiol/Herbals	104	34	55	15
Cannabidiol	4,227	147	131	3,949
Cannabinoid, Synthetic (Nos)	19	10	9	0
Cannabinol	26	17	3	6
Cannabis Sativa Flowering Top	389	259	109	21
Cannabis Sativa Seed Extract	4	4	0	0
Cannabis Sativa Seed Oil/Device/Herbals	1	1	0	0
Cannabis Sativa Seed Oil	32	13	15	4
Cannabis Sativa Seed	5	5	0	0
Cannabis Sativa Subsp. Indica Top/Device	22	14	6	2
Cannabis Sativa Subsp. Indica Top	4,039	2,369	1,277	393
Cannabis Sativa Whole	2	1	1	0
Delta-8-tetrahydrocannabinol/Device/Herbals/Nicotine	4	3	0	1
Delta-8-tetrahydrocannabinol/Device/Herbals	66	37	23	6
Delta-8-tetrahydrocannabinol/Herbals	5	2	2	1
Delta-8-tetrahydrocannabinol	44	19	15	10
Delta-9-tetrahydrocannabinolic Acid	12	8	2	2
Dronabinol	1,342	750	487	105
Hemp	31	14	12	5
Nabilone	319	95	172	52
Nabiximols	39	13	23	3
∑ (with duplicates)	10,832	3,871	2,379	4,582
Cannabis Case Reports (without duplicates)	**10,687**	3,771	2,346	4,570

Overview about the number of cannabis case reports sorted by gender and cannabis product.

3.1.3 Case Reports Containing Cannabis Products Divided into Subgroups

The classification in between THC and CBD products is necessary in order to be able to differentiate side effects of THC and CBD, as the two substances differ a lot in their pharmacological properties. Table 18, based on table 5, gives an overview about the number of case reports containing specific cannabis products.

Table 18. Number of Case Reports in FAERS Divided by CBD, THC or Both, CBD & THC.

Cannabis Product	Cannabis Group	Number of Cases	Number of Cases ≥ 50 Years Old
Cannabidiol/Cannabis Sativa Seed Oil	CBD	27	10
Cannabidiol/Device/Herbals	CBD	17	3
Cannabidiol/Herbals/Menthol	CBD	2	0
Cannabidiol/Herbals	CBD	104	31
Cannabidiol	CBD	4,227	31
Cannabis Sativa Seed Extract	CBD	4	0
Cannabis Sativa Seed Oil/Device/Herbals	CBD	1	0
Cannabis Sativa Seed Oil	CBD	32	8
Cannabis Sativa Seed	CBD	5	0
Hemp	CBD	31	4
∑		4,450	87
11-Hydroxy-delta-9-tetrahydrocannabinol	THC	6	0
11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	THC	22	4
Cannabinoid, Synthetic (Nos)	THC	19	1
Cannabinol	THC	26	1
Delta-8-Tetrahydrocannabinol	THC	44	3
Delta-8-tetrahydrocannabinol/Device/Herbals/Nicotine	THC	4	1
Delta-8-tetrahydrocannabinol/Device/Herbals	THC	66	9
Delta-8-tetrahydrocannabinol/Herbals	THC	5	1
Delta-9-tetrahydrocannabinolic Acid	THC	12	0
Dronabinol	THC	1,342	320
Nabilone	THC	319	158
∑		1,865	498
Cannabidiol/Delta-8-Tetrahydrocannabinol/Device/Herbals	Both	10	0
Cannabidiol/Delta-8-Tetrahydrocannabinol	Both	16	2
Cannabis Sativa Flowering Top	Both	389	59
Cannabis Sativa Subsp. Indica Top	Both	4,039	420
Cannabis Sativa Subsp. Indica Top/Device	Both	22	3
Cannabis Sativa Whole	Both	2	0
Nabiximols	Both	39	15
∑		4,517	499

The table gives an overview about the cannabis case reports in FAERS divided into the 3 subgroups, 'CBD', 'THC' and 'Both', depending on what is the main component or which substance is most likely to have similar effects.

Since the focus of this thesis are older people, once again the case reports for people being 50 years and older were selected. In general, there are various definitions and age limits when talking about older adults (Kowal & J Edward Dowd, 2001; World Health Organization, 2020a).

It was decided together with the advisor to set the age limit to 50 years though. The number of case reports, where people are 50 years and older, are written in column four. Sometimes the age was not defined in years, but in decades, months, or days. It was necessary to standardize the age information to 'years', before classifying various age groups (e.g. 18.250 days correspond to 50 years). After classification, one receives 4,450 CBD cases, 1,865 THC cases and 4,517 cases that are related to both THC and CBD. The proportion of people being 50 years and older consuming CBD to all CBD cases is around 2%, with THC it lies around 27% and with CBD and THC around 11%.

3.1.4 Case Reports Containing Prescribed Cannabis Products

Table 19 gives a good overview about the number of case reports containing prescribed cannabis products. As already described in chapter 2.4.2.1 the search was not only for the brand name of cannabis products, namely the terms 'Canemes', 'Cesamet', 'Epidiolex', 'Marinol', 'Syndros' and 'Sativex', but also for some drug names, like 'nabilone', 'dronabinol' and 'nabiximols'.

Table 19. Prevalence of Prescribed Cannabis Products.

		Age			Gender		
Prescribed Cannabis Products	# of all Reports	≥ 50	< 50	not specified	male	female	not specified
Canemes	0	0	0	0	0	0	0
Cesamet	128	58	25	44	23	75	30
Nabilone	192	100	58	34	72	98	22
Epidiolex	**3,946**	4	71	**3,871**	55	35	**3,856**
Marinol	**466**	**171**	118	177	218	223	25
Syndros	37	10	3	24	19	17	1
Dronabinol	**850**	142	557	157	522	249	79
Sativex	0	0	0	0	0	0	0
Nabiximols	39	15	15	9	13	23	3
∑ Prescribed Cannabis Products	**5,658**	**500**	847	4,316	**922**	**720**	4,016

The brand name of cannabis products and the drug name nabilone, dronabinol and nabiximols were included when analyzing prescribed cannabis products. Neither was cannabidiol, which is available without any prescription as well.

All in all, 5,658 cases with medically prescribed cannabis have been found. In almost all cases cannabis was reported as suspected product leading to side effects. 500 cases were reported among people being 50 years and older, 847 cases were reported in the younger generation and no age was defined for the remaining reported cases. The majority of case reports containing medically prescribed cannabis products, more precisely 71%, also did not show any information about gender. Most of the cases contain Epidiolex as suspect product (3,946

cases), whereby around 98% of the cases have neither a defined age nor a defined gender. In second place of the most frequently prescribed medicinal cannabis preparations is dronabinol with a frequency of 850 cases. Those case reports did not contain any information about the used brand. Brand names that contain dronabinol as a medicinal substance, for example 'Marinol' and 'Syndros' are listed separately. The number of cases containing the term 'nabilone' tends to be higher in those people over 50 years of age, but 'dronabinol' cases are generally more reported in younger patients. However, these statements are not necessarily reliable because a large proportion of the reports do not have any information about the age. The highest number of case reports containing prescribed cannabis products was reported by the USA, followed by Canada, followed by Australia.

3.2 Reactions and Side Effects

3.2.1 Summary of Reaction Categories

Side effects and reactions mentioned in cannabis case reports were sorted by four different reaction classes. Table 20 shows the prevalence of reactions in people over 50 years consuming cannabis for any reason, either medicinally or recreationally, whereas table 21 focuses on the prevalence of reactions in people over 50 years consuming prescribed cannabis products for medical purposes.

Basically, cannabis users over 50 years of age, whether they consumed cannabis recreationally or medicinally, primarily suffer from neuropsychiatric side effects. Medically prescribed cannabis users show those effects slightly more (29.60% of the case reports) than cannabis users, who consumed cannabis for any reason (27.24% of the case reports). As already suggested, these neuropsychiatric side effects can be traced back to THC. However, this is only an assumption since the number of CBD cases generally is very low. Despite the low number of CBD cases, it looks as if occuring reactions in CBD case reports are a bit more balanced among the reaction classes than in THC cases, where the trend is in neuropsychiatric side effects. Cardiovascular side effects and infections are slightly more common in over 50 years old people, who use cannabis recreationally and medicinally. When used medicinally, there are around 4% fewer cardiovascular side effects and around 2% fewer infections. However, sedation is a more common side effect when cannabis is taken in the form of a medicinal preparation (2.40%) than for an unspecified reason (1.87%). A comparison between the various cannabis products can hardly be made because Epidiolex and Sativex cases are

rarely reported, especially in those over 50 years of age. Almost only reports of nabilone and dronabinol cases remain.

Table 20. Prevalence of Reaction Groups in People Over 50 years Consuming Cannabis Either Medically or Recreationally.

Reaction Groups	# of cases only in this category	Prevalence	CBD	THC	Combined
Cardiovascular Side Effect	103	9.61%	10	23	70
Neuropsychiatric Disease	292	27.24%	14	143	135
Infection	78	7.28%	9	33	36
Sedation	20	1.87%	3	10	7
Unsure	42	3.92%	7	26	9
Reaction Groups	**# of cases in this category which are combined with other categories**	**Prevalence**	**CBD**	**THC**	**Combined**
Cardiovascular Side Effect	146	13.62%	10	61	75
Neuropsychiatric Disease	203	18.94%	13	130	60
Infection	131	12.22%	6	72	52
Sedation	55	5.13%	2	31	22
Unsure	7	0.65%	0	4	3

*All together there are 986 cases assigned to a category. 86 cases are not assigned to any category e.g. 'drug ineffective', 'drug interaction', 'product formulation issue'. Those are not mentioned in this analysis. Prevalence: Number of People with Reaction / Number of People ≥ 50 years with cannabis consumption * 100.*

Table 21. Prevalence of Reaction Groups in People Over 50 years Consuming Prescribed Cannabis for Medical Reasons.

Reaction Groups	# of prescribed cases only in this category	Prevalence	Canemes/ Cesamet/ Nabilone	Epidiolex	Marinol/ Syndros/ Dronabinol	Sativex/ Nabiximols
Cardiovascular Side Effect	27	5.40%	2	0	19	6
Neuropsychiatric Disease	148	29.60%	53	0	88	7
Infection	27	5.40%	1	0	26	0
Sedation	12	2.40%	2	0	10	0
Unsure	18	3.60%	8	0	10	0
Reaction Groups	**# of cases in this category which are combined with other categories**	**Prevalence**	**Canemes/ Cesamet/ Nabilone**	**Epidiolex**	**Marinol/ Syndros/ Dronabinol**	**Sativex/ Nabiximols**
Cardiovascular Side Effect	62	12.40%	26	0	36	0
Neuropsychiatric Disease	129	25.80%	74	0	55	0
Infection	79	15.80%	55	0	24	0
Sedation	43	8.60%	23	0	20	0
Unsure	5	1.00%	0	0	5	0

*All together there are 249 cases assigned to a category. 251 cases are not assigned to any category e.g. 'drug ineffective', 'drug interaction', 'product formulation issue'. Those are not mentioned in this analysis. Prevalence: Number of People with Reaction / Number of People ≥ 50 years with medical consumption * 100.*

Often it is not possible to assign case reports to a single reaction category, as consumers report many different side effects and reactions. It is noticeable that there are basically more cases where people over 50 years report reactions in various categories of side effects. Neuropsychic side effects occur more often alone than in combination with cardiovascular side effects, infections, and sedation.

3.2.2 Frequently Reported Reactions

In order to further analyse the frequency of reported reactions, a comparison between three different subgroups, namely cannabis users over 50 years of age (table 22), medical cannabis users over 50 years of age (table 23) and medical cannabis users under 50 years of age (table 24) was made. A list, which shows all possible reactions together with its frequency is available under request. Only the most common side effects will be mentioned in the tables below. These side effects have occurred with a frequency of more than 5%.

When looking at cannabis case reports from people over 50 years of age, regardless of whether cannabis was used medicinally or recreationally, some reactions or side effects are reported very frequently. These include, listed with decreasing frequency, all types of pain (13.15%), completed suicide (9.05%), fatigue (7.37%), dizziness (7.18%), vomiting (7.18%) and any kind of swelling (7.18%). However, cannabis preparations are particularly indicated for pain and vomiting. Perhaps these reactions are still simply listed because patients have this side effect despite taking cannabis preparations.

Table 22. Frequently Reported Side Effects of Medical and Recreational Cannabis in People of 50 Years of Age or Older.

Reactions	#	%	# of CBD-Product	# of THC-Product	# of Combined
Completed suicide	97	9.05%	0	16	81
Dizziness (including: dizziness postural)	77	7.18%	7	47	18
Fatigue	79	7.37%	7	50	22
Pain (including: abdominal pain, abdominal pain upper, back pain, bone pain, chest pain, eye pain, oral pain, oropharyngeal pain, pain in extremity, painful respiration, pleuritic pain, procedural pain, spinal pain, stoma site pain)	141	13.15%	6	60	75
Swelling (including: eye swelling, lip swelling, peripheral swelling, joint swelling, pharyngeal swelling)	56	5.22%	3	9	44
Vomiting (including vomiting projectile)	77	7.18%	9	52	17

All in all, 1.072 cannabis cases have been reported. This table not only shows the frequency of important side effects in number of cases (#) and percentage of cases (%), but also which group of cannabis products lead to the described reactions, either CBD, THC or both. Meaning of colors: light red - frequency of side effect in between 5 and 10%; dark red - frequency of side effect greater than 10%

In case reports that contain medically prescribed cannabis (table 23) vomiting was mentioned with an even higher frequency (10%), closely followed by dizziness (9.80%) and fatigue (9.80%). Other frequently reported neuropsychiatric side effects are altered mood (9.20%), cognitive disorder (9.20%) and confusional state (6%). Fibromyalgia and sacroilitis are reported with a frequency of 9.20%, asthenia of 5.20%, decreased appetite of 7.60%, diarrhoea of 7.40%, hypotension of 5.40% and weight decreased of 5.60%. The reactions are again due to THC derivatives, since CBD and nabiximols cases usually have no information on age, as already mentioned in the previous chapters.

When younger people take medicinal cannabis products, reactions other than those described above are common (table 24). In the under-50s, accidental overdoses (6.26%), coma (5.31%), depression (5.55%), pulmonary edema (7.32%), seizures (5.90%) and vomiting (7.44%) are frequently reported. Even if it is medically prescribed cannabis, one can still not rule out that it is a matter of drug abuse. Accidental overdoses and coma in younger patients, often iatrogenically caused by intoxication, suggest abuse.

Table 23. Frequently Reported Side Effects of Prescribed Cannabis in People of 50 Years of Age or Older.

Reactions	#	%	Canemes/ Cesamet/ Nabilone	Epidiolex	Marinol/ Syndros/ Dronabinol	Sativex/ Nabiximols
Asthenia	26	5.20%	8	0	18	0
Cognitive disorder	46	9.20%	46	0	0	0
Confusional state	30	6.00%	8	0	22	0
Decreased appetite	38	7.60%	16	0	22	0
Diarrhoea	37	7.40%	7	2	28	0
Dizziness (including dizziness postural)	49	9.80%	29	0	20	0
Fatigue	49	9.80%	6	0	41	2
Fibromyalgia	46	9.20%	46	0	0	0
Hypotension (including orthostatic hypotension)	27	5.40%	23	0	3	1
Mood altered	46	9.20%	46	0	0	0
Sacroiliitis	46	9.20%	46	0	0	0
Somatic symptom disorder	46	9.20%	46	0	0	0
Vomiting (including vomiting projectile)	50	10.00%	10	0	40	0
Weight decreased	28	5.60%	3	0	25	0

All in all, 500 prescribed cannabis cases have been reported. This table not only shows the frequency of important side effects in number of cases (#) and percentage of cases (%), but also which cannabis product lead to the described reactions. Meaning of colors: light red - frequency of side effect in between 5 and 10%; dark red - frequency of side effect greater than 10%

Table 24. Frequently Reported Side Effects of Prescribed Cannabis in People Younger than 50 Years of Age.

Reactions	#	%	Canemes/ Cesamet/ Nabilone	Epidiolex	Marinol/ Syndros/ Dronabinol	Sativex/ Nabiximols
Accidental overdose	53	6.26%	0	0	53	0
Coma	45	5.31%	0	3	43	0
Depression	47	5.55%	4	0	41	2
Pulmonary oedema	62	7.32%	0	0	62	0
Seizure	50	5.90%	4	15	30	1
Vomiting	63	7.44%	2	7	50	4

All in all, 847 prescribed cnnabis cases have been reported. This table not only shows the frequency of important side effects in number of cases (#) and percentage of cases (%), but also which cannabis product lead to the described reactions. Meaning of colors: light red - frequency of side effect in between 5 and 10%; dark red - frequency of side effect greater than 10%

3.3 Presumable Interactions

There are various criteria that are often used in practice to prevent side effects and interactions. However, these critera have low agreement between each other, low sensitivity and low specificity, which is problematic from a clinical perspective. Thus the predictive value of side effects varies (Abarca et al., 2004; Brown et al., 2016).

Since the prediction of side effects is not precise and some side effects are not found in clinical studies prior to product launch, the importance of pharmacovigliance has increased significantly in recent years. Investigations of drug interactions and side effects after drug approval, the so-called phase four, have become indispensable. The analysis of case reports that are collected in databases like FAERS and that are publicly available is very important in pharmacovigilance. These case reports are particularly important when coming from a population that is less considered in clinical studies. In particular, old and sick patients, who are an important subgroup using medical cannabis, are often excluded from clinical studies. Table 33 (appendix) shows possible pharmacokinetic interactions and table 34 (appendix) possible synergistic pharmacodynamic reactions of cannabis ingredients (THC, CBD, nabiximols) and drugs that appear in cannabis case reports of people being 50 years and older.

3.3.1 Presumable Pharmacokinetic Interactions Between Cannabis and Other Drugs

When looking at the pharmacokinetic interactions shown in table 33 (appendix) it is noticable that of the 593 drugs mentioned in the case reports, 352 drugs presumably interact with CBD, 342 with THC and 314 with nabiximols. As previously indicated, nabiximols, the combination of THC and CBD, has a slightly different metabolism compared to THC and CBD itself, when we

rely on the information from Drugbank. It is already certain that CBD reduces the strong hallucinogenic effects of THC (Karschner et al., 2011). However, it is not clear whether the metabolism changes as well, as shown by pharmacokinetic data of Drugbank, or whether other interactions of nabiximols are simply not explored. Dosage of THC and CBD plays and important role, though. In general, the majority of the presumable interactions are due to interactions with CYP3A4, followed by P-Gp, CYP2D6, CYP2C9 and CYP2C19.

It is assumed that when two drugs interact with the same enzyme, they can be expected to influence each other's metabolism. This interaction takes place when both are substrates that can displace one another from the binding pocket or when one of the substances is an inhibitor or inductor. One have to take into account, however, that this makes sense in theory, but can work very differently in practice.

Interestingly, mostly the same drugs might interact with THC and CBD. However, some drugs might indicate an interaction with CBD but not with THC. These include atropine, cefaclor, entacapone, fenfluramine, memantine, mycophenolic acid, oxazepam, spironolactone, telmisartan and trospium. Nabiximols might have fewer pharmacokinetic interactions, but not always the same as THC. Unlike nabiximols, THC probably does not interact with entcapone, fenfluramine, memantine, telmisartan and trospium.

3.3.2 Presumable Synergistic Pharmacodynamic Reactions Between Cannabis and Other Drugs

The ‘Pharmacodynamic Interactions Table’ (table 34 in the appendix) shows that 193 out of 593 drugs lead to cardiovascular side effects with a frequency between 1 and 10%, 47 drugs even with a frequency over 10%. 196 drugs induce neuropsychiatric side effects with a frequency of 1 to 10%, 115 drugs with a higher frequency than that. 166 drugs might lead to infections with a frequency of 1 to 10%, 69 drugs even with a higher frequency. Sedation is less reported with the drugs mentioned. Only 96 drugs cause this side effect in between 1 and 10%, 35 drugs with a higher frequency.

57 drugs show side effects of common (>1%) or very common (>10%) frequency in each of the examined reaction classes, namely aripiprazole, baclofen, bevacizumab, bisoprolol, brimonidine, buprenorphine, bupropion, carvedilol, cetirizin, cetuximab, citalopram, diazepam, escitalopram, fentanyl, gabapentin, gemcitabine, hydrocodone, imatinib, indapamide, interferon beta-1a, lenalidomide, letrozole, levetiracetam, losartan, lurasidone, meloxicam, memantine, methylphenidate, mirtazapine, modafinil, mycophenolic acid,

naproxen, nifedipine, nivolumab, olanzapine, oxaliplatin, oxcarbazepine, oxybutynin, oxycodone, paliperidone, paroxetine, posaconazole, pregabalin, quetiapine, risperidone, rivastigmine, rofecoxib, ropinirole, selegiline, sotalol, tamsulosin, terazosin, tramadol, varenicline, vemurafenib, venlafaxine and zolpidem.

However, this does not take into account drugs that lead to reactions without any defined frequency. If the frequency is undefined, one can expect it to be low. Drug information that report side effects without any frequency were treated as if no reaction occurs. This is because the focus should be on the drugs that cause a certain side effect with a higher frequency and not less than 1%.

As described in chapter 2.2.2.2, strong synergistic pharmacodynamic interactions between cannabis ingredients (CBD, THC, nabiximols) and the medicinal substances mentioned in the case reports are examined in the next step. Strong synergistic reactions have been defined in a way that the sum of the frequencies of both interacting substances within a reaction class must be at least '3', whereas '1' stands for common side effects and '2' for very common side effects. There are a few presumable synergistic pharmacodynamic interactions between THC/CBD/nabiximols and drugs mentioned in FAERS case reports. The numbers of those synergistic interactions are listed in table 25.

Table 25. Number of Presumable Pharmacodynamic Interactions Between Cannabis and Other Drugs.

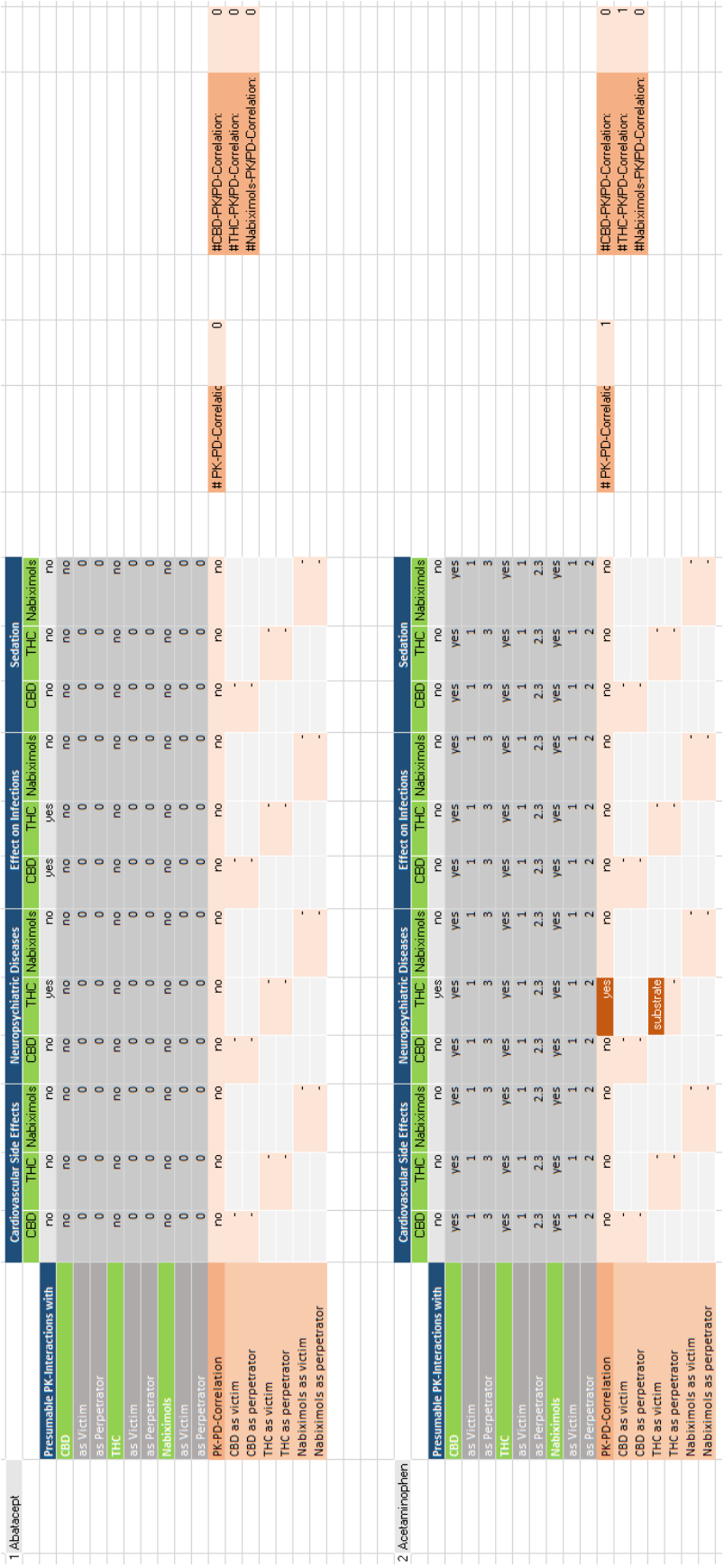
Side Effect Category	Cardiovascular Side Effects			Neuropsychiatric Diseases			Effect on Infections			Sedation		
Cannabis Product	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols
Number of Presumable Interactions	0	47	47	115	311	115	235	69	0	131	0	35

The interaction to 593 drugs has been examined.

3.3.3 Correlation of Pharmacokinetic and Pharmacodynamic Interactions [x]

These tables provide an overview of the pharmacokinetic and pharmacodynamic interactions of all the drugs that were mentioned in FAERS together with CBD/THC/nabiximols. It indicates when the pharmacokinetic interactions may correlate with the pharmacodynamic ones. If there is a correlation, the table also describes whether cannabis is acting as a victim or a perpetrator. Since three cannabis preparations are examined in combination with drug x in four different reaction categories, theoretically up to 12 correlations can exist. There can be a maximum of four correlations per cannabis ingredient, one for each of the four side effect

classes. The prerequisite for the correlation is that both pharmacokinetic interactions and synergistic pharmacodynamic interactions take place in between two drugs. The procedure is explained in detail by the first two tables in Excel, shown in figure 8.



1 Abatacept

Presumable PK-Interactions with	Cardiovascular Side Effects			Neuropsychiatric Diseases			Effect on Infections			Sedation		
	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols
CBD	no	no	no	no	yes	no	yes	yes	no	no	no	no
as Victim	no	no	no	no	no	no	no	no	no	no	no	no
as Perpetrator	0	0	0	0	0	0	0	0	0	0	0	0
THC	0	0	0	0	0	0	0	0	0	0	0	0
as Victim	no	no	no	no	no	no	no	no	no	no	no	no
as Perpetrator	0	0	0	0	0	0	0	0	0	0	0	0
Nabiximols	0	0	0	0	0	0	0	0	0	0	0	0
as Victim	no	no	no	no	no	no	no	no	no	no	no	no
as Perpetrator	0	0	0	0	0	0	0	0	0	0	0	0
PK-PD-Correlation	no	no	no	no	no	no	no	no	no	no	no	no
CBD as victim	-			-			-			-		
CBD as perpetrator	-			-			-			-		
THC as victim		-	-		-	-		-	-		-	-
THC as perpetrator		-	-		-	-		-	-		-	-
Nabiximols as victim			-			-			-			-
Nabiximols as perpetrator			-			-			-			-

# PK-PD-Correlatic	0

#CBD-PK/PD-Correlation:	0
#THC-PK/PD-Correlation:	0
#Nabiximols-PK/PD-Correlation:	0

2 Acetaminophen

Presumable PK-Interactions with	Cardiovascular Side Effects			Neuropsychiatric Diseases			Effect on Infections			Sedation		
	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols	CBD	THC	Nabiximols
CBD	no	no	no	no	yes	no	no	no	no	no	no	no
as Victim	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
as Perpetrator	1	1	1	1	1	1	1	1	1	1	1	1
THC	3	3	3	3	3	3	3	3	3	3	3	3
as Victim	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
as Perpetrator	1	1	1	1	1	1	1	1	1	1	1	1
Nabiximols	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3
as Victim	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
as Perpetrator	1	1	1	1	1	1	1	1	1	1	1	1
PK-PD-Correlation	2	2	2	2	2	2	2	2	2	2	2	2
CBD as victim	no	no	no	no	yes	no	no	no	no	no	no	no
CBD as perpetrator	-			-			-			-		
THC as victim		-			substrate			-			-	
THC as perpetrator		-			-			-			-	
Nabiximols as victim			-			-			-			-
Nabiximols as perpetrator			-			-			-			-

# PK-PD-Correlatic	1

#CBD-PK/PD-Correlation:	0
#THC-PK/PD-Correlation:	1
#Nabiximols-PK/PD-Correlation:	0

Figure 8. Correlation of Pharmacokinetic and Pharmacodynamic Interactions of abatacept and acetaminophen. *Correlation exists as soon as there is at least one pharmacokinetic and pharmacodynamic interaction.*

Abatacept exhibits synergistic pharmacodynamic interactions in combination with THC on the neuropsychiatric and infectious level and with CBD on the infectious level, but both cannabis ingredients do not lead to any pharmacokinetic interaction. This is why there is no correlation between the interactions of the examined drugs. In comparison, acetaminophen is considered in more detail. It is stated that THC together with acetaminophen can lead to synergistic side effects on a neuropsychiatric level. Pharmacokinetic interactions also apply that THC acts both as perpetrator (inhibitor, inductor) and as victim (substrate). The pharmacokinetic-pharmacodynamic correlation is therefore '1', because only one of the 12 columns have both kinds of interaction.

The pharmacokinetics and pharmacodynamics of drugs mentioned in table 26 often correlate with either THC, CBD or nabiximols (correlation=3).

Table 26. Drugs that have a High Chance to Interact with Cannabis on a Pharmacodynamic and Pharmacokinetic Way.

Cannabis Product	High Chance of Interaction With
CBD	Bupropion, cetirizine, clonazepam, diazepam, fentanyl, lenalidomide, levetiracetam, lurasidone, mycophenolic acid, olanzapine, oxcarbazepine, oxybutynin, oxycodone, paroxetine, peginterferon alfa-2b, pirfenidone, posaconazole, quetiapine, risperidone, ropinirole, rucaparib, selegeline, sotalol, sunitinib, tacrolimus, tapentadol, tramadol, vemurafenib, venetoclax, venlafaxine
THC	Amphetamine, corticotropin, crizotinib, cyclosporine, dasatinib, enzalutamide, everolimus, gemcitabine, posaconazole, vemurafenib
Nabiximols	Clonidine, clozapine

Drugs in the right column have a chance to interact both, via the pharmacokinetic pathway and via the pharmacodynamic pathway as well with cannabis ingredients. Only those drugs with a high correlation are mentioned.

3.3.4 Presumable Interactions Between Cannabis and Diseases

Diseases have a significant influence on the tolerability of cannabis preparations. On the one hand, patients with a certain disease may take drugs that interact with cannabis preparations. On the other hand, the disease itself can have an impact, either in a pharmacokinetic way, if the enzyme equipment or metabolism changes for example in the case of liver disease, or pharmacodynamically, if the effects of the disease are further potentiated by cannabis. This would be the case if for example a patient with heart failure suffers from additional cardiovascular side effects due to cannabis consumption.

Since the FAERS database hardly provides any information about the patient's disease ('Reason for Use'-column) or this information is often missing, it is not possible to carry out a

statistical analysis of connections between cannabis use and diseases. Information about co-diseases can often be found in the case narratives, which, as already made clear at the beginning, were not requested for this thesis due to lack of time. In future research, these case narratives would have to be inquired and analyzed in order to be able to make statements about drug-disease interactions with cannabis preparations.

However, it can be assumed that diseases with similar reactions to cannabis can produce synergistic side effects in combination with cannabis products (see chapter 1.1.4.2). Usage of cannabis should also be reconsidered in the event of a malfunction of cannabis-metabolizing enzymes due to any disease.

3.4 Interesting Drugs

All drugs that appear in the cannabis case reports are potentially responsible for the reported reaction or side effect. Drugs that have been reported frequently in combination with cannabis are particularly interesting for closer analysis. The more often a drug is reported together with a cannabis ingredient, the higher the likelihood that these two substances will interact with each other. In addition to the frequency, the calculated potential correlation between pharmacokinetic and pharmacodynamic interactions and information from clinical studies and interaction programs are also taken into account. A drug is classified as interesting as soon as it is reported frequently but does not provide any information about drug-drug interactions.

3.4.1 Frequently Reported Drugs

The following tables list drugs that are reported in cannabis case reports to the extent of at least 5%. Table 27 shows cases of people greater or equal 50 years of age and table 28 under 50 years of age. In addition, it is also indicated which cannabis preparations are taken in combination with the listed drugs, in most cases these are THC derivatives (nabilone, dronabinol). Numbers highlighted in light red indicate a frequency of at least 5%, dark red at least 10%. The main focus is on drugs that are reported more often in older people than in younger ones.

Fentanyl, gabapentin, hydromorphone, lorazepam, morphine and tramdadol are frequently reported in both age groups. Apart from the drugs just mentioned, remaining frequently reported drugs differ in between the age groups. It is noticeable among those people under

50 years that they often take medically prescribed cannabis in combination with drugs or substances that are said to have an addictive effect (ethanol, amphetamine, metamphetamine, cocaine, benzodiazepine like alprazolam, clonazepam, diazepam and lorazepam) or drugs, which point out an existing addiction disorder (for example methadone). It is quite likely that cannabis will be misused in these patients, even if the drug has been prescribed.

Table 27. Frequently Reported Drugs Mentioned in Prescribed Cannabis Case Reports of People Being 50 Years and Older.

Drugs	Brand Name or Product that contains drug from column A	#	%
Amitriptyline		57	11.40%
Aspirin	Percodan	42	8.40%
Baclofen	Lioresal	33	6.60%
Cisplatin		32	6.40%
Clozapine	Clozaril	27	5.40%
Cyclophosphamide	Cytoxan	33	6.60%
Dexamethasone	Decadron	32	6.40%
Doxorubicin	Adriamycin	32	6.40%
Duloxetine	Cymbalta	65	13.00%
Etanercept		46	9.20%
Etoposide		26	5.20%
Fentanyl	Subsys, Duragesic	28	5.60%
Furosemide	Lasix	26	5.20%
Gabapentin	Neurontin	94	18.80%
Hydromorphone	Dilaudid	34	6.80%
Lorazepam	Ativan	88	17.60%
Metoclopramide	Mcp, Reglan	40	8.00%
Morphine	Ms Contin	33	6.60%
Omeprazole	Prilosec	27	5.40%
Ondansetron	Zofran	44	8.80%
Pantoprazole	Protonix	95	19.00%
Pregabalin	Lyrica	25	5.00%
Quetiapine	Seroquel	51	10.20%
Quinine		40	8.00%
Tramadol	Ixprim	58	11.60%

Overview about drugs that are reported often (>5%) together with cannabis products in people of 50 years of age and older. The number of all prescribed cannabis case reports of people ≥50 years is 500. Meaning of colors: light red – frequency ≥5%; dark red – frequency ≥10%

Table 28. Frequently Reported Drugs Mentioned in Prescribed Cannabis Case Reports of People Being Under 50 Years.

Drugs	Brand Name or Product that contains drug from column A	#	%
Acetaminophen	Dafalgan, Cocodamol	122	14.40%
Alprazolam	Xanax	83	9.80%
Amphetamine		57	6.73%
Buprenorphine		91	10.74%
Citalopram	Celexa	57	6.73%

Clonazepam	Klonopin	85	10.04%
Cocaine		62	7.32%
Codeine	Cocodamol, Fiorinal With Codeine	66	7.79%
Diazepam	Valium	135	15.94%
Ethanol	Alcohol	64	7.56%
Fentanyl	Subsys, Duragesic	64	7.56%
Gabapentin	Neurontin	57	6.73%
Hydrocodone	Lortab, Vicodin, Norco, Xodol	47	5.55%
Hydromorphone	Dilaudid	44	5.19%
Lorazepam	Ativan	50	5.90%
Methadone	Dolophine	133	15.70%
Methamphetamine		44	5.19%
Morphine	Ms Contin	147	17.36%
Olanzapine	Zyprexa	48	5.67%
Oxycodone	Oxycontin, Percocet	166	19.60%
Tramadol	Ixprim	55	6.49%

Overview about drugs that are reported often (>5%) together with cannabis Product in people under 50 years of age. The number of all prescribed cannabis case reports of people ≥50 years old is 847. Meaning of colors: light red – frequency ≥5%; dark red – frequency ≥10%

3.4.2 Finding a Trend in Cannabis Interactions

Abnormalities or pecularities regarding CBD, THC and nabiximols in combination with frequently mentioned drugs were analyzed in the following chapters to identify possible drug-drug interactions. The focus was on drugs that were reported more often in older people than younger ones. 'Interaction checker' from www.drugs.com (Drugs.com, 2020b) and 'Wechselwirkungscheck' from www.doccheck.com (DocCheck Community GmbH, 2020) have been used as interaction programs.

3.4.2.1 CBD-Cases

Basically, the focus of CBD cases was on people of undefined age, since in most of the cases no age was reported. Therefore, it is not possible to make statements about age-specific interactions of CBD with concomitant drugs. Nevertheless, drugs that were perceived as interesting, have been highlighted.

First of all, ascorbic acid needs to be mentioned. Even if there is a general misconception that vitamins do not cause problems in the body, for sure they impair essential functions in the human body. The interaction program does not show any interaction between ascorbic acid and CBD, but still there are 168 cases, that report side effects when taking, among other substances, the combination of vitamin C together with CBD. There exists a similar situation with another vitamin - vitamin D. A relatively high number of cases have been reported, but

there is no data about occurring interactions. It would be interesting to find out if both substances interact with one another. Minerals and salts are also perceived to be less toxic to the body, but this is not true. They regulate the ion exchange and play an important role in vital physiological processes. It is likely that calcium and its salts, that are mentioned in 57 CBD cases, interact with CBD. Clonidine in combination with CBD was mentioned in 70 case reports. The drug is indicated for sedation, high blood pressure, ADHD and cancer pain. The interaction program warns of neuropsychiatric reactions, the previously created 'Pharmacokinetic-Pharmacodynamic-Correlation Table' warns as well by predicting interactions in between clonidine and CBD. However, no clinical data could be found when searching the literature, even though more than 1% of the reported CBD cases contain this drug. The drug fluticasone and its equivalent salt fluticasone propionate are of particular interest. These substances are listed separately in the table because their pharmacokinetics were also treated separately on Drugbank. 68 cases of undefined age were reported. Although the interaction program does not detect any interaction and no clinical data are available, pharmacokinetic and pharmacodynamic interactions have been predicted. This drug is therefore interesting for future studies. Folic acid was reported 46 times. It provides no suspected interactions, no information on the interaction program and no studies on the combination with CBD. Levothyroxine was reported in combination with CBD in 67 cases. No data on interactions are available here, which is why a future investigation of interactions would be recommendable. Melatonin also appears very often in the CBD reports. A side effect is reported 104 times when CBD is taken in combination with melatonin, among other drugs. No interaction is predicted and no interaction is known in between CBD and melatonin. It is possible that it is often reported in combination with CBD because it has a similar indication and is used for the same purpose. Montelukast, a drug used for allergies and asthma prevention, is mentioned 55 times in CBD case reports. No interactions are reported here eighter. Omeprazole, a proton pump inhibitor, might be interesting for future studies. It has been reported 62 times. According to the interactions checker, the combination of omeprazole and CBD "may increase side effects such as drowsiness, diarrhea, decreased appetite, and liver problems" (Drugs.com, 2020b). However, clinical studies say that omeprazole has no influence on Sativex concentration (Stott et al., 2013). Although the study claims that omeprazole has no effect on CBD, this combination still remains of interest because the interaction can take place the other way round. CBD would therefore act as the perpetrator, which turns out to be entirely possible

when looking at the pharmacokinetic data. A similar case occurs with oxcarbazepine. Together with CBD it might lead to moderate interactions in the neuropsychiatric area. However, clinical studies rule out an interaction. One paper states that CBD oral solution has no influence on the concentration of oxcarbazepine (Gaston et al., 2017). Like with omeprazole, an interaction the other way round with CBD as victim has not been examined here either. Data from interaction programs and clinical studies for interactions in between phenytoin and CBD provide different information. Interactions checker says that co-administration may reduce the blood levels and effects of CBD (Drugs.com, 2020b). In clinical studies it is said that CBD oral solution has no influence on the concentration of phenytoin (Gaston et al., 2017). The role of CBD as victim is not discussed here either. Another drug that aroused interest is polyethylene glycol, a substance that is often used against constipation. 116 cases containing CBD together with polyethylene glycol have been reported. There are not only calculated probable interactions but also known interactions available on the interaction program. However, a clinical study would provide better information about interactions. Like polyethylene glycol, CBD can also cause diarrhea, which is an interesting side note. Ranitidine, an antihistamine and antacid, is reported relatively frequently and data about its pharmacokinetics and pharmacodynamics suggest interactions. However, there are no known interactions between CBD and ranitidine. In the case of risperidone, interactions are mentioned on the interaction program, but no clinical studies have been found. THC, on the other hand, has interaction studies together with risperidone.

Some drugs are mentioned often in CBD case reports but are less interesting for various reasons. First, certain drugs might be often reported together with CBD, not because they interact with each other, but because they are indicated for the same reason. These drugs include besides others, abatacept, for rheumatoid arthritis, baclofen, for muscle spasms, gabapentin and lacosamide, for seizures. Although carbamazepine has a very similar indication to CBD with seizures and nerve pain, interactions between the two substances have also been reported. The interaction program speaks of a reduced CBD concentration in the blood, which leads to a reduced effectiveness of CBD. In clinical studies it was found that CBD oral solution has no influence on the concentration of carbamazepine, though (Gaston et al., 2017). Even with lamotrigine, which is indicated for seizures and bipolar disorder, the interaction program points out possible neuropsychiatric interactions. However, one study shows that CBD has no influence on the concentration of lamotrigine (Gaston et al., 2017).

Levetiracetam, also an anti-epileptic drug, has been reported 487 times. Clinical studies rule out that CBD has an influence on levetiracetam (Devinsky et al., 2018; Gaston et al., 2017). This is probably also the reason why it is often used in combination with CBD.

Another reason, why some frequently mentioned drugs were not considered as important is because interactions with CBD are already known. Physicians and healthcare providers know that they need to be careful with co-administration or even consider avoidance. These drugs include cetirizine, diazepam, esomeprazole, ibuprofen, lorazepam and zonisamide. Detailed description of the interaction can be found in the Excel file [x] under request.

Some drug interactions have already been ruled out in clinical studies, which is why they are of no interest for further investigation. According to a clinical study, CBD oral solution has no influence on the concentration of clonazepam (Gaston et al., 2017). Nevertheless, 285 cases were reported with this drug combination, among others. Perhaps, this is exactly the reason for its frequent co-administration. Since these substances are considered to be mutually compatible, they are often taken in combination and therefore often reported together. The same paper also excludes an interaction in between CBD and phenobarbital. There are different clinical trials about topiramte. In one study, CBD oral solution is said to have no effect on topiramate (Devinsky et al., 2018). In the second study, Epidiolex is said to significantly increase the serum concentration of topiramate (Gaston et al., 2017). Thus caution is advised when coadministered. With valproic acid, there are three different studies that speak of no interaction with CBD (Devinsky et al., 2018; Gaston et al., 2017; Morrison et al., 2019). Although there appears to be no interaction, many cases are reported. The results of the clinical studies probably lead to the fact that the drugs are often administered together. Table 29 summarizes drugs that are interesting or are not in future interaction studies with CBD.

Table 29. Interesting Drugs in CBD-Case Reports.

INTERESTING	NOT INTERESTING
Ascorbic acid, vitamin D, calcium, clonidine, fluticasone (fluticasone propionate), folic acid, levothyroxine, melatonin, montelukast, omeprazole, oxcarbazepine, phenytoin, polyethylene glycol, ranitidine, risperidone	<u>Same indication as CBD:</u> Abatacept, baclofen, gabapentin, lacosamide, carbamazepine, lamotrigine, levetiracetam <u>Already known interactions with CBD:</u> Cetirizine, diazepam, esomeprazole, ibuprofen, lorazepam, zonisamide <u>Studies available about interaction of CBD with:</u> Clonazepam, topiramate, phenobarbital, valproic acid

Frequently mentioned drugs in CBD case reports which are or are not interesting for future studies.

3.4.2.2 THC-Cases

The reported THC cases are best suited for analyzing the defined research question. The aim is to identify a trend in older adults, more precisely those over 50 years of age, with regard to drug-drug interactions in between THC and frequently mentioned drugs. For this not only data from over 50 years old people is needed but also from the younger ones to be able to make a comparison. Sufficient data is available for both age groups, which makes the analysis of THC more meaningful.

Interesting drugs that are reported more frequently in older adults in combination with THC, but for which no data on interactions are known, are ampicillin (ratio of case reports with people ≥50 years old to <50 years old: 16:0), aspirin (39:18), the most potent neuroleptic on the European market benperidol (9:0), cisplatin (32:13), citric acid (7:1), cyclophosphamide (33:21), darbapoetin alfa (11:0), dexamethasone (31:5), esomeprazole (13:3), etoposide (26:8), famotidine (6:1), fludrocortisone (13:0), glipizide (9:1), granisetron (9:5), levetiracetam (8:4), levothyroxine (22:1), magnesium (12:0), metamizole (9:0), metformin (14:2), ondansetron (43:21), pantoprazole (62:14), pentamidine (8:2), prednisone (9:5), quinine (24:1), sargramostim (8:0), sodium bicarbonate (10:0), sodium chloride (8:0), sulbactam (14:0), trimethoprim (11:8), vemurafenib (7:1) and zuclopenthixol (9:0).

Due to common pharmacodynamic interactions, synergistic interactions are predicted for certain drugs. These drugs are for example atorvastatin (13:1), bromazepam (10:1), flupentixol (16:0), lorazepam (88:43), pipamperone (11:0), quetiapine (40:32), spironolactone (15:1) and tacrolimus (9:1). Dexamethasone and sulbactam might be of particular interest since both drugs increase the risk of infections, what THC does as well. They might act synergistically.

With clozapine there are animal studies saying that THC does not change the concentration of clozapine in the brain of mice and therefore clozapine is not a P-Gp substrate (Brzozowska et al., 2017). The interaction program warns of neuropsychiatric side effects when taking this drug combination. As no clinical data on human studies were found and no study is known where THC acts as a victim and clozapine as perpetrator, further studies are pending. There is an in-vitro study of doxorubicin together with THC, which states that THC makes no considerable inhibition of P-Gp, where doxorubicin is a substrate (Zhu et al., 2006). THC could also represent the victim and thus interact with doxorubicin as perpetrator. Respectively, only the interaction via the P-Gp was investigated in the study. However, both drugs have other

common metabolizing enzymes as well, such as CYP3A4, via which an interaction could take place. There is also a clinical study for the combination of THC and omeprazole with the result that omeprazole has no influence on Sativex concentration (Stott et al., 2013). As with the drugs before only the effect of THC as perpetrator was measured without looking at THC viewed as victim. Another important drug to mention is risperidone. Interactions from animal studies are already known here. THC increases P-Gp expression, which leads to a lower concentration of risperidone and 9-OH-risperidone in the brain in mice (Brzozowska et al., 2017). Despite the fact that risperidone is not recommended in combination with THC, it is reported relatively frequently (16 cases in people ≥50 years of age, 14 cases in younger people). However, there are still no interaction studies in humans existing.

As in the chapter on CBD cases, there are similar reasons for THC cases why frequently reported drugs are classified as less interesting for future studies. With some drugs, interactions are already known. Amitryptiline, aripiprazole, chlorpromazine, clonidin, dimenhydrinat, duloxetine, hydromorphone, mirtazapine, paroxetine, pregabalin, prochlorperazine, sertraline, tramadol and trazodone might lead to neuropsychiatric side effects like dizziness, drowsiness, confusion and difficulty with concentrating when taken together with THC (Drugs.com, 2020b). Amlodipine, metoprolol, nifedipine or propranolol may lead to addictive effects in lowering the blood pressure, headache, dizziness, lightheadedness, fainting and/or change in pulse or heart rate (Drugs.com, 2020b). Zolpidem together with THC may increase the blood levels and this may increase side effects as drowsiness, diarrhea, decreased appetite and liver problems (Drugs.com, 2020b). For dextromethorphane there is an in-vitro study which says that THC inhibits CYP2D6, where dextromethorphan is a substrate (Yamaori, Okamoto et al., 2011). The interaction program also warns of neuropsychiatric interactions with THC. Gabapentin has been reported 91 times in older patients and 52 times in younger patients. An animal study in mice has shown that THC and gabapentin act synergistically in states of neuropathic pain (Atwal et al., 2019). Gabapentin “enhances the anti-allodynic actions of THC and improves its therapeutic window”(Atwal et al., 2019, p. 115). The indications are seizures and pain, as it is the case with THC. Next drug is vincristine. According to an in-vitro study, THC inhibits ABCC1 in MRP1, where vincristine is a substrate (Holland et al., 2008). There are also existing data about warfarin, that has been shown to interact with THC in in-vitro studies. The first study says that THC inhibits CYP2C9, where S-warfarin is substrate (Yamaori et al., 2012). The second study

warns against combined drug use of cannabis and warfarin, which might increase the risk of bleeding (Damkier et al., 2019). This is because “THC inhibits the CYP2C9-mediated metabolism of warfarin” (Damkier et al., 2019, p. 28).

Some drugs that are often co-medicated with THC are of less interest because they are reported more often in younger people than in older ones. These drugs often have a mood-enhancing or calming effect but can also be associated with addictive behavior. They therefore do not necessarily lead to reactions in younger patients more often but are simply consumed more frequently. One can also assume that THC, although medically prescribed, is still misused in these patients. Drugs that are more commonly reported in young patients include alprazolam, amphetamine, benzodiazepine, benzoylecgonine, buprenorphine, caffeine, citalopram, clonazepam, cocaine, codeine, diamorphine, diazepam, dihydrocodeine, escitalopram, ethanol, fentanyl, flunitrazepam, hydrocodone, lidocaine, meperidine, methadone, methamphetamine, methylphenidate, midomafetamine, morphine, naloxone, nicotine, nordazepam, olanzapine, oxazepam, oxycodone, oxymorphone, phenobarbital, promethazine, temazepam and venlafaxine. In addition, acetaminophen, carisoprodol, diphenhydramine, naproxen, tenofovir and testosterone are more frequently reported in combination with THC in young people.

In general, when combining benzodiazepines with THC, it can be observed that some drugs in this group were reported more frequently in older people (lorazepam), while some were more frequently reported in younger people (nordazepam, oxazepam, temazepam). This is probably also related to the physicians' prescribing pattern. Nevertheless, some drugs, which are reported more often in cases with older than with younger people, are also of less interest. This is because the high frequency is often not due to the higher risk of interactions with THC, but rather to the increased prescribing and use of the preparations by older people. This mainly includes drugs that are associated with age-specific diseases such as Alzheimer's Disease, Parkinson's Disease or COPD. Those drugs are amantadine, carbidopa, donepezil, entacapone, formoterol, levodopa, pramipexole, rivastigmine and tiotropium. Bisacodyl and loperamide are probably also taken more frequently by older people. The assumption is that older patients often suffer from constipation due to the high number of medications.

If a drug has an indication similar to THC, the physician may intentionally combine both substances, drug X and THC, in order to lower their single dose and take advantage of the synergistic effect. Therefore, drugs that are reported more often than others in combination

with THC should not be perceived as harmful combinations straight away. The following drugs are not only reported often together with THC but also have similar indications. Amisulpride, aprepitant and metoclopramide, for example, have an anti-emetic effect. Baclofen is used as a muscle relaxant, just like THC is used in combination with CBD. Carbamazepine is used against spasms and seizures, etanercept is used against autoimmune diseases such as rheumatoid arthritis, and piritramide is used against pain. All of these indications are also found with cannabis and cannabis ingredients. Table 30 summarizes which drugs are of interest for interaction studies with THC and which are not.

Table 30. Interesting Drugs in THC-Case Reports.

INTERESTING	NOT INTERESTING
Ampicillin, aspirin, benperidol, cisplatin, citric acid, cyclophosphamide, darbapoetin alfa, dexamethasone, esomeprazole, etoposide, famotidine, fludrocortisone, glipizide, granisetron, levetiracetam, levothyroxine, magnesium, metamizole, metformin, ondansetron, pantoprazole, pentamidine, prednisone, quinine, sargramostim, sodium bicarbonate, sodium chloride, sulbactam, trimethoprim, vemurafenib, zuclopenthixol, atorvastatin, bromazepam, flupentixol, lorazepam, pipamperone, quetiapine, spironolactone, tacrolimus, dexamethasone, sulbactam, clozapine, doxorubicin, omeprazole, risperidone	<u>Already known interactions with THC:</u> Amitriptyline, aripiprazole, chlorpromazine, clonidine, dimenhydrinate, duloxetine, hydromorphone, mirtazapine, paroxetine, pregabalin, prochlorperazine, sertraline, tramadol, trazodone, amlodipine, metoprolol, nifedipine, propranolol, zolpidem, dextromethorphan, gabapentin, vincristine, warfarin <u>In combination with THC more consumption in younger people:</u> Alprazolam, benzodiazepine, benzoylecgonine, buprenorphine, caffeine, citalopram, clonazepam, cocaine, codeine, diamorphine, diazepam, dihydrocodeine, escitalopram, ethanol, fentanyl, flunitrazepam, hydrocodone, lidocaine, meperidine, methadone, methamphetamine, methylphenidate, midomafetamine, morphine, naloxone, nicotine, nordazepam, olanzapine, oxazepam, oxycodone, oxymorphone, phenobarbital, promethazine, temazepam, venlafaxine, acetaminophen, carisoprodol, diphenhydramine, naproxen, tenofovir, testosterone <u>In combination with THC more consumption in older people:</u> Amantadine, carbidopa, donepezil, entacapone, formoterol, levodopa, pramipexole, rivastigmine, tiotropium, bisacodyl, loperamide <u>Same indication as THC:</u> Amisulpride, aprepitant, metoclopramide, baclofen, carbamazepine, etanercept, piritramide

Frequently mentioned drugs in THC case reports which are or are not interesting for future studies.

3.4.2.3 Nabiximols-Cases

Unfortunately, very few cases of nabiximols are reported per se. Of course, one could conclude from this that there are generally hardly any side effects with nabiximols in combination with CBD. The results for drugs that interact with nabiximols are therefore limited. Duplicates can also be assumed, which makes statistical analysis even more unreliable.

Nevertheless, some drugs exist, which are reported in combination with nabiximols and do not provide good or any information about existing interactions, namely acetaminophen, dalfampridine, human interferon beta, methylprednisolone, ocrelizumab and pantoprazole. For baclofen there exists a warning for neuropsychiatric side effects on the interaction program. Drugs like amlodipine and pregabalin do appear in FAERS case reports, although interactions are already known. Drugs with known interactions are less relevant for this research thesis. Equally less interesting are cases where the drug is frequently reported in cases of people under 50 years of age. This includes escitalopram, fingolimod and prednisone. Table 31 summarizes interesting and uninteresting drugs for closer interaction studies with nabiximols.

Table 31. Interesting Drugs in Nabiximols-Case Reports.

INTERESTING	NOT INTERESTING
Acetaminophen, baclofen, dalfampridine, human interferon beta, methylprednisolone, ocrelizumab, pantoprazole	Already known interactions with nabiximols: Amlodipine, pregabalin In combination with nabiximols more consumption in younger people: Escitalopram, fingolimod, prednisone

Frequently mentioned drugs in nabiximols case reports which are or are not interesting for future studies.

3.4.3 Comments on Results

Most of the drugs that are frequently featured in FAERS reports, have been either examined in interaction studies or have been found in interaction programs, that provide information about interactions. Regarding interaction programs, it has to be said that www.doccheck.com hardly shows any interactions, which are available www.drugs.com. Also, sometimes data from papers and interaction programs do not match. For example, considering interactions with THC, the results differ for clozapine (paper says there is no interaction whereas interaction program says there is), diclofenac and vincristine (paper claims interaction whereas interaction program does not), and others.

When drugs are mentioned frequently it does not necessarily mean that this drug leads to more side effects in combination with cannabis. A good reason for frequent reporting can also be the fact that the drug is taken more frequently in general or that patients who need to take medical cannabis need to take additional drugs for the same indications as well. If there are no studies or data on drugs that are often taken in combination with cannabis, it should be in the interests of researchers to carry out studies with these substances in order to be able to rule out an interaction.

3.5 Individual Case Reports

Since a statistical evaluation of side effects in cannabis case reports is not possible, individual case reports have been analyzed. These reports were selected through a search strategy as described in chapter 2.4.2.4.

The case reports were roughly divided into cardiovascular side effects, neuropsychiatric side effects, side effects related to infections, side effects related to sedation, reports of people with extremely high age and reports with an extremely high number of drugs. The figures in this chapter are shown in greater detail in a power point presentation [x], which can be obtained on request. The figures provide brief information about the person mentioned, such as age, sex or co-illness. Drugs ingested are listed on the left-hand side, the reaction or side effect that has been caused is shown on the right-hand side. Some interactions are represented by arrows in color. The gray arrows between drugs and reactions indicate which drugs presumably caused the reaction. Side effects, interactions and indications have only been mentioned, if they might be important for the case itself. As already mentioned in earlier parts of the thesis, no analysis of the full case narratives could be carried out. Although this was defined in advance as aim three of the thesis, requesting full case reports was no longer feasible due to the corona pandemic and time restrictions. This makes it impossible to do a good analysis, since information about drug dosage, drug application form, co-disease, patient history etc. is missing.

3.5.1 Cardiovascular Side Effects

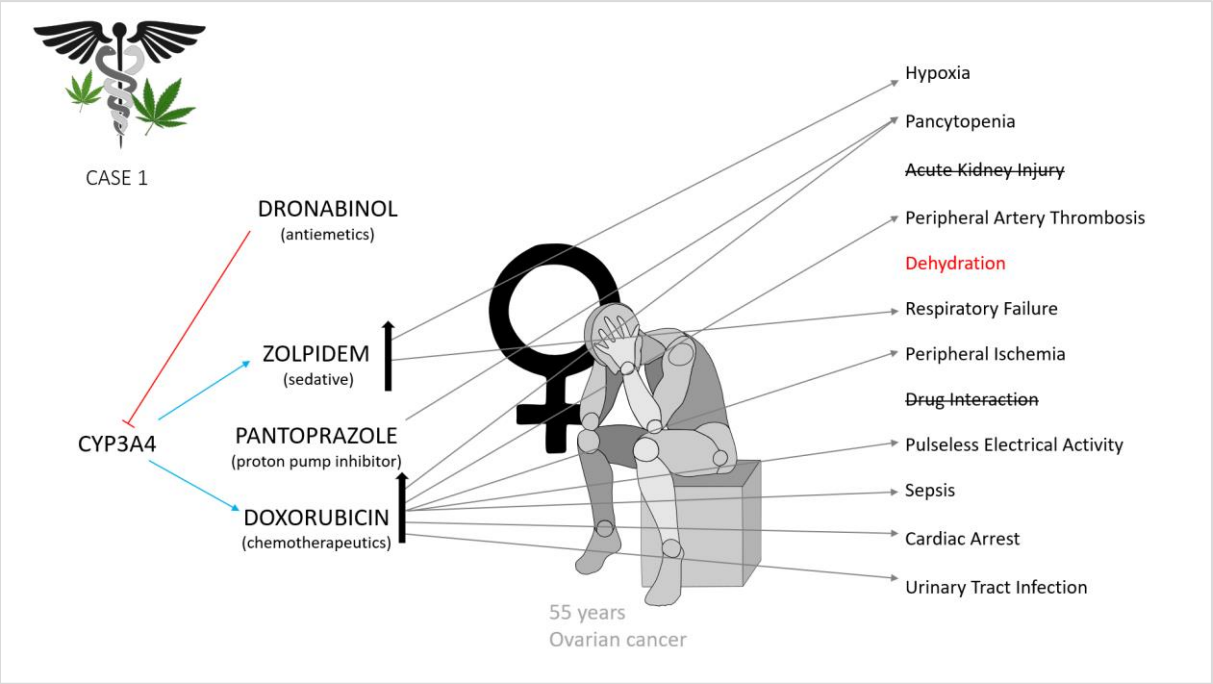


Figure 9. Case Report 1. *Presentation of the drugs taken and reported side effects.*

In the first case (figure 9) a 55-year-old woman who suffered from ovarian cancer has been described. She took the synthetic THC analogue and antiemetic dronabinol, the sedative zolpidem, the proton pump inhibitor pantoprazole, and the chemotherapeutic agent doxorubicin. The reported side effects are shown on the right hand-side in the graphic. Due to occuring reactions, case 1 is assigned to group ‘cardiovascular side effects’, although it could have also been classified to the group ‘infections’. This is because side effects cannot be strictly assigned to one category. Looking at the side effects one can guess that hypoxia and respiratory failure have been probably caused by zolpidem. This assumption comes from the fact that a study observed “a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% […] in patients with mild to moderate sleep apnea when treated with zolpidem compared to placebo” (Sanofi-Aventis U.S. LLC, 2019, p. 2). Pantoprazole was assigned to pancytopenia because this side effect was cited in post-marketing research for pantoprazole (Pfizer, 2019). ‘Acute kidney injury’ and ‘drug interaction’ have not been taken into account because the patient's previous history or more precise information on the intake procedure is not known. Dehydration is a reaction that cannot be deducted from any drug. Even if the prescribing information about dronabinol does not state that it causes cardiovascular side effects, we know very well about THC, which is a component of nabiximols, that it does cause changes in

pulse rate and blood pressure, cardiac arrhythmias and palpitations (GW Pharma Ltd., 2019). It is therefore assumed that dronabinol also induces these side effects to a certain extent. When analyzing the pharmacokinetic data, the following things have been found. Doxorubicin interacts with the P-Gp. In order to determine whether THC inhibits this transporter, an in-vitro study has been carried out. It turned out that THC makes no considerable inhibition of P-Gp, where doxorubicin is a substrate (Accord Healthcare GmbH, 2017; Tournier et al., 2010). Limitations of this study are first, that this is no clinical study and second, that THC also inhibits CYP3A4, where doxorubicin is a substrateas well. Not only doxorubicin, but also zolpidem is a substrate of CYP3A4. When the enzyme is inhibited by THC (dronabinol), the metabolism of zolpidem and doxorubicin might be reduced, which might lead to an increased drug concentration and consequently a higher likelihood of side effects. The increased doxorubicin concentration probably leads to the described cardiovascular side effects. In conclusion, dronabinol may have a pharmacokinetic impact on other drugs via various enzymes. Even though one interaction has been excluded, there are other possible ways of interactions to consider.

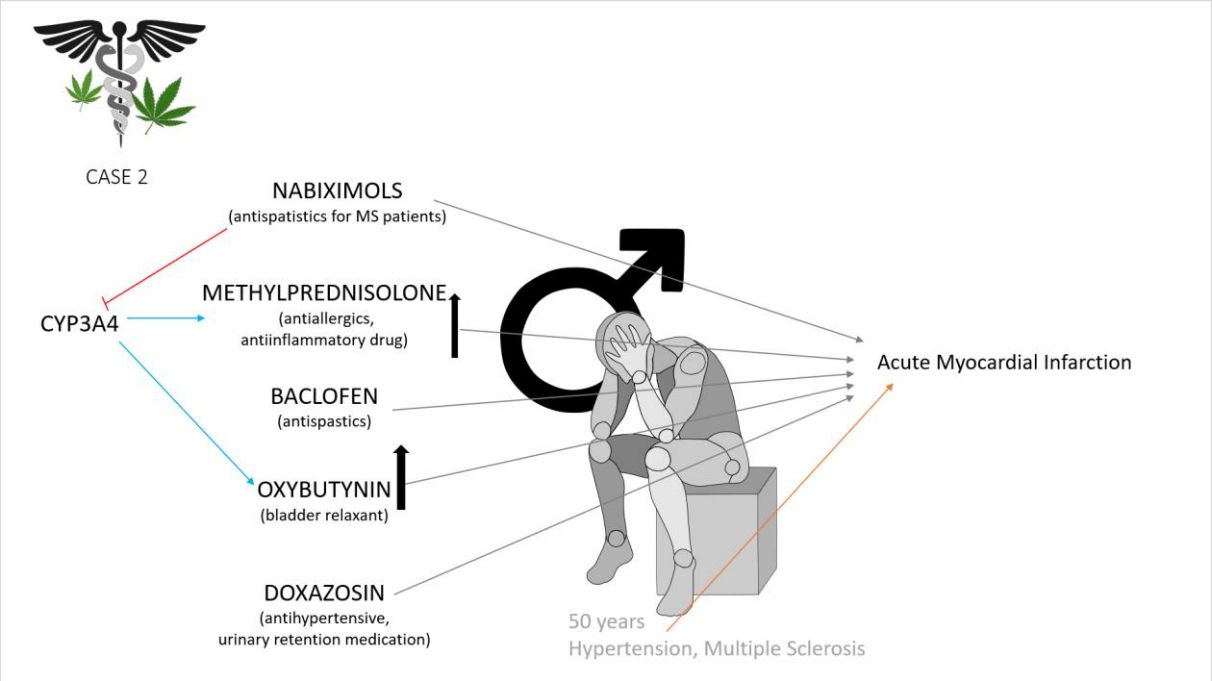


Figure 10. Case Report 2. *Presentation of the drugs taken and reported side effects.*

The second case (figure 10), which has been assigned to the group of cardiovascular side effects, is about a 50-year-old man that suffered from hypertension and multiple sclerosis. The drugs he took include nabiximols, which is indicated for spasms in multiple sclerosis, methylprednisolone an anti-inflammatory drug, baclofen, an antispastics, oxybutynin, a

bladder relaxant and doxazosin, an antihypertensive and urinary retention medication. This case has been reported because the man had an acute myocardial infarction. All the drugs mentioned and the fact that the patient already has been diagnosed with hypertension favor this outcome. Looking at the prescribing information from nabiximols, it becomes clear that nabiximols leads to alterations in pulse rate and blood pressure and that it is therefore not recommended in patients with serious cardiovascular diseases (GW Pharma Ltd., 2019). The prescribing information of the other drugs also warn of an increased cardiovascular risk (Pfizer, 2011; Ratiopharm GmbH, 2019; STADApharm GmbH, 2015, 2019). In addition to the pharmacodynamic interactions, pharmacokinetic interactions are also determined. Nabiximols inhibits CYP3A4, which is responsible for the metabolism of methylprednisolone and oxybutynin. Reduced degradation might lead to increasing concentration and finally result in intensified cardiovascular side effects. Both, pharmacokinetic and pharmacodynamic interactions play a role, which are often correlated with one another.

3.5.2 Neuropsychiatric Side Effects

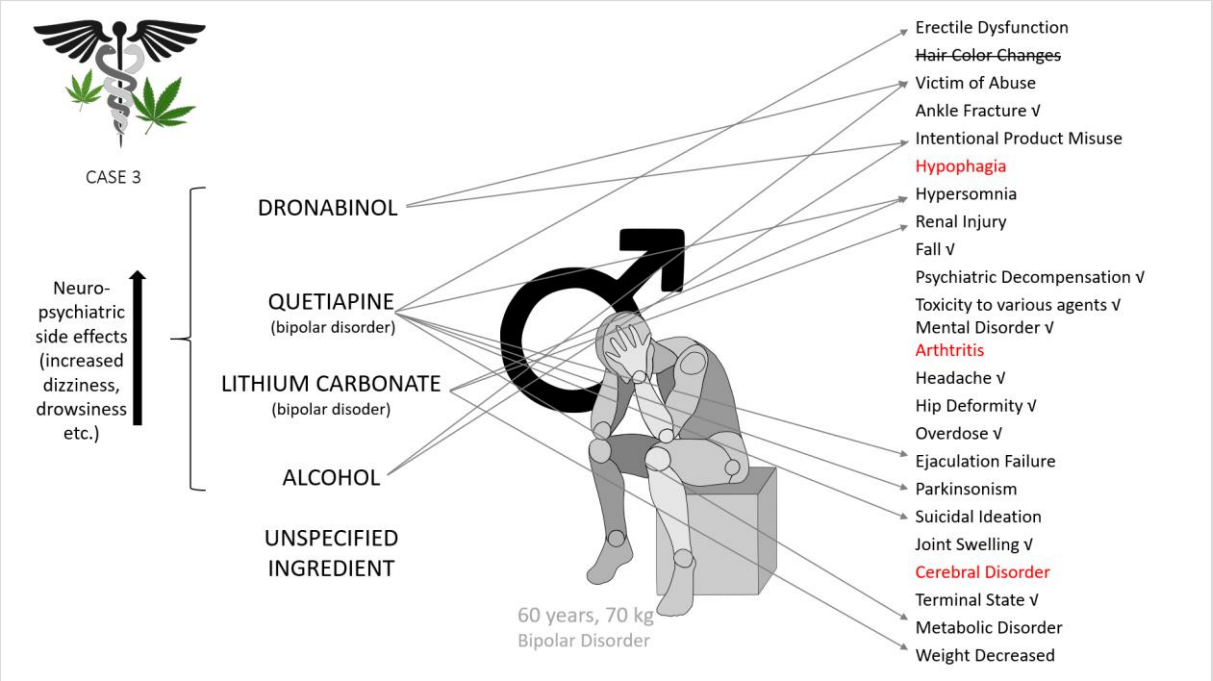


Figure 11. Case Report 3. *Presentation of the drugs taken and reported side effects.*

A case of a 60-year-old man suffering from bipolar disorder has been reported (figure 11). Dronabinol was used for an unknown reason but it might be indicated for off-label use against bipolar disorder. The patient took quetiapine and lithium carbonate for this disease as well. In

addition, he also consumed alcohol and an unspecified ingredient. Many side effects have been reported, the majority of those can be attributed to neuropsychiatric side effects.

In the prescribing information of Marinol (dronabinol) it is stated that dronabinol use should be avoided in patients with a psychiatric history (Patheon Softgels Inc., 2017). Dronabinol might be indicated for bipolar disorder as off-label use, though. However, it is relevant to consider that “patients with a history of substance abuse or dependence, inluding marijuana or alcohol, may be more likely to abuse Marinol as well” (Patheon Softgels Inc., 2017, p. 4). With quetiapine it is noticeable that it is contra-indicated in combination with CYP3A4 inhibitors, which not only includes THC but also ethanol. In the prescribing information it is written that the dose of quetiapine has to be padded in older people. Many people have misused quetiapine, especially if they have been alcohol dependent in the past (Accord Healthcare Limited & Glenmark Arzneimittel GmbH, 2017). In general, the psychoactive drugs might influence each other in a very negative way. Increased neuropsychiatric side effects, such as dizziness, drowsiness and others might occur. The consequences of this might have been mental disorders, frequent falls, fractures and injuries. These reactions are marked with a tick in the graphic. No clear statements could be made about the cause of the reactions marked in red, namely hypophagia, arthritis and cerebral disorder.

The remaining question is why this 60-year old patient received medically prescribed cannabis, although interactions with the other substances are already known. There are even contraindications. The data could be incorrect in the sense that the patient took recreational cannabis instead of dronabinol. This is not negligible because alcohol consumption already shows a certain tendency towards drug addiction. In general, it can be said that both alcohol and THC increase the psychoactive side effects of the drugs and the disease itself and that the use of cannabis in this case is very risky.

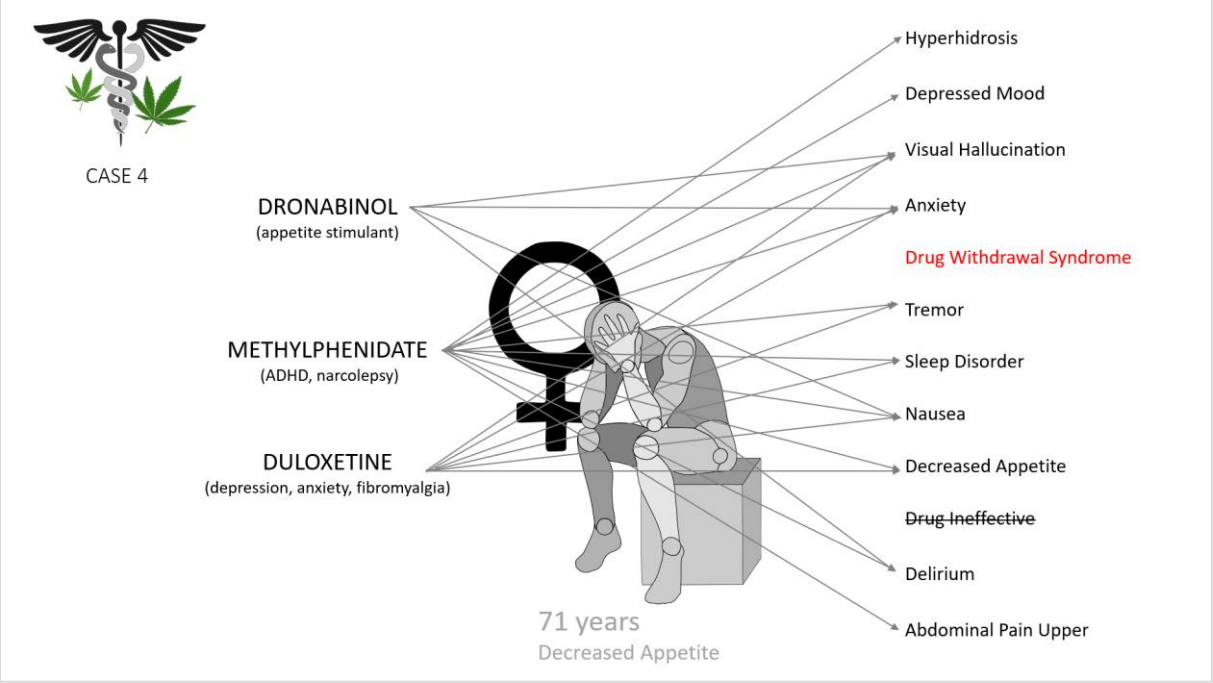


Figure 12. Case Report 4. *Presentation of the drugs taken and reported side effects.*

The next case report (figure 12) that has been analyzed in detail also falls under the category of neuropsychiatric side effects. It is about a 71-year-old woman who had decreased appetite and who therefore used dronabinol medically. As a comedication she took methylphenidate, which is used in both ADHD and narcolepsy, and duloxetine, which is used in depression, anxiety and fibromyalgia. A wide range of side effects, such as depressed mood, anxiety, sleep disorder or decreased appetite, were reported, although drugs have already been taken against it. That probably means that the corresponding drug was not sufficiently effective, which is also noted in the reactions as 'drug ineffective'. No specific cause can be found with one reported reaction, namely 'drug withdrawal syndrome'. When looking at the prescribing information, the following things were noticed. With methylphenidate, hyperhidrosis, tremor and nausea are reported much more frequently in studies on older people. Those reactions have also been reported in this 71-year-old patient. In addition, it is not allowed to use methylphenidate in older patients at all, because efficacy and safety are not given in over 60-year-old people. It is also noted that methylphenidate lowers the metabolism of some antidepressants. It is not known whether methylphenidate has an effect on the antidepressant duloxetine, though (Ratiopharm GmbH, 2018b). Duloxetine's prescribing information only states that there are no clinical data about interactions with other neuropsychiatric drugs, but that precaution should be taken (Ratiopharm GmbH, 2020). In principle, methylphenidate is

not a suitable medication. In combination with the other two mentally active substances, THC and duloxetine, synergistic pharmacodynamic interactions are further intensified.

3.5.3 Infection

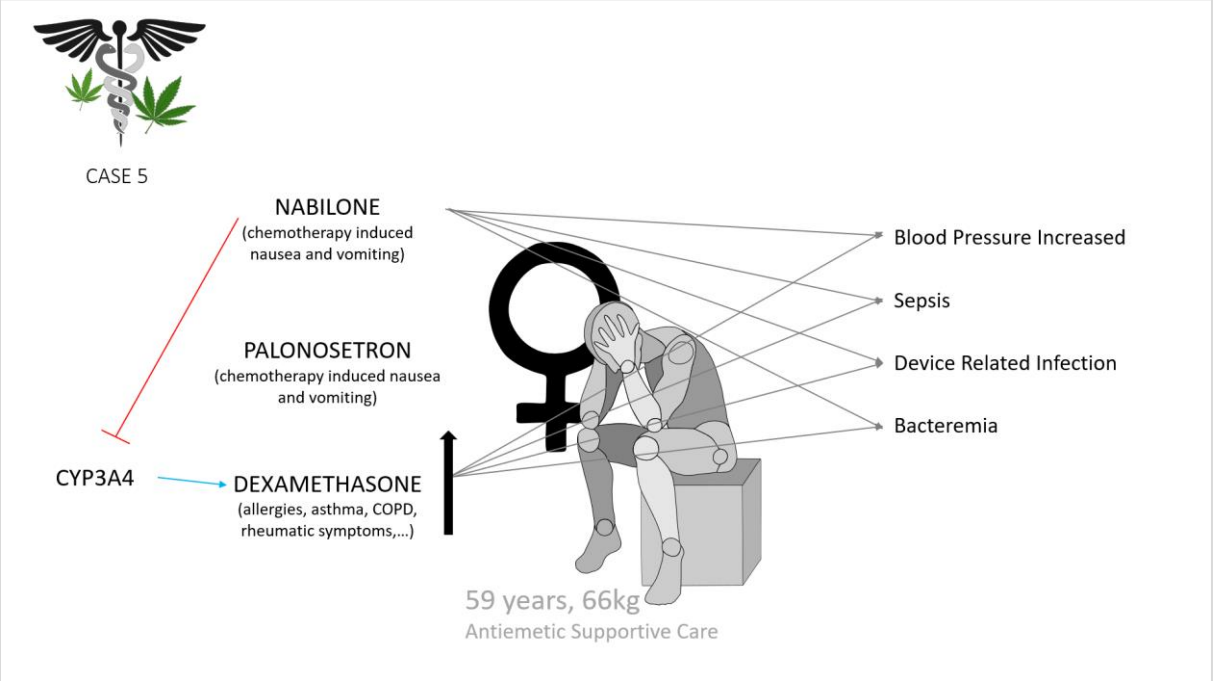


Figure 13. Case Report 5. *Presentation of the drugs taken and reported side effects.*

The following case report (figure 13) is about a 59-year-old woman, who took drugs for anti-emetic supportive care. The woman might be a cancer patient, since she took nabilone and palonosetron, which are both indicated against chemotherapy induced nausea and vomiting. Additionally, she also took dexamethasone, which is indicated against allergies, asthma or COPD, for example. Except the increase of blood pressure, all reported reactions deal with infection. Nabilone and dexamethasone were probably mainly responsible for the mentioned side effects (Ratiopharm GmbH, 2018a; Valeant Pharmaceuticals International, 2006). Nevertheless, it can be assumed that the patient also received chemotherapy, which of course also increases the susceptibility to infections. Nabilone and dexamethasone act synergistically on the pharmacodynamic level. However, both can interact on a pharmacokinetic level as well. Nabilone inhibits CYP3A4, an important enzyme that, among other things, metabolizes dexamethasone (Ratiopharm GmbH, 2018a). If the enzyme is inhibited, the dexamethasone concentration might increase and this can lead to more severe side effects. No reported side effects can be attributed to palonosetron.

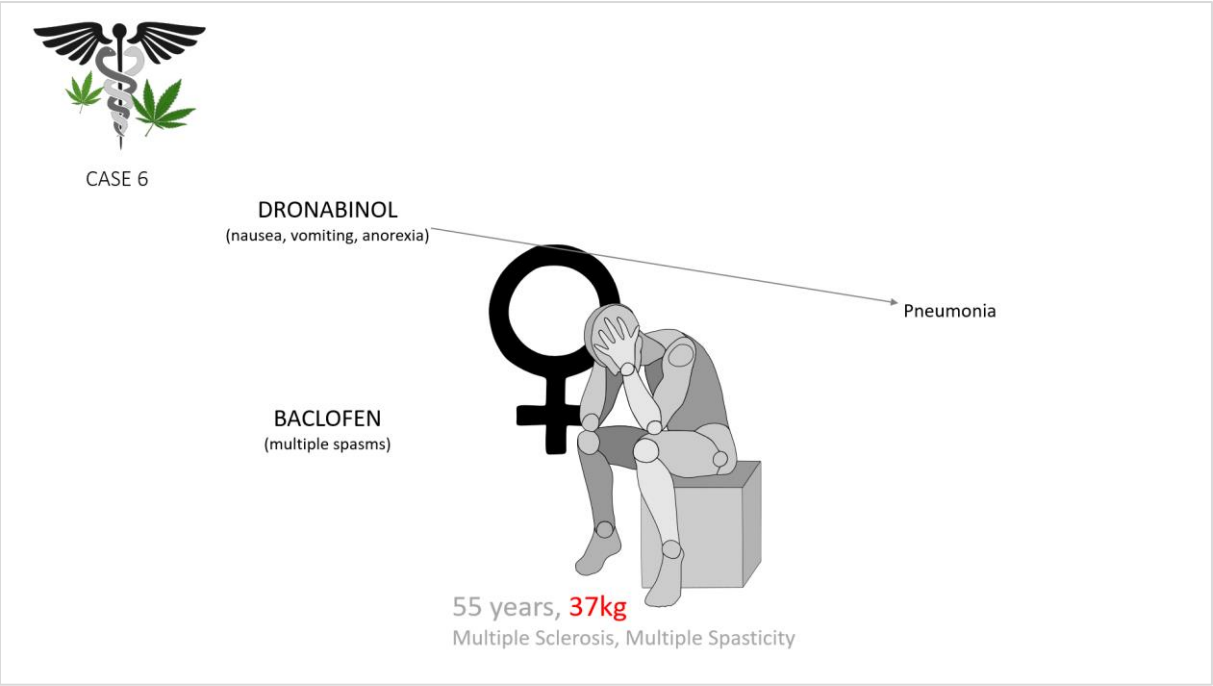


Figure 14. Case Report 6. *Presentation of the drugs taken and reported side effects.*

Case 6 (figure 14) describes a 55-year-old woman with multiple sclerosis and multiple spasticity. When looking at the patient data, it is noticeable that the patient is underweight with 37 kg. Maybe that is why she took dronabinol, which is not only indicated for nausea and vomiting, but also for anorexia. Another reason for her dronabinol prescription might be her disease, since dronabinol is also used off-label for spasms coming from multiple sclerosis. Besides this cannabis product she also took baclofen, which helps with multiple spasms. In the prescribing information of dronabinol it is written that dronabinol should only be given carefully to patients suffering from seizures. The patient should be monitored and therapy should be discontinued if seizures occur (Patheon Softgels Inc., 2017). The only outcome reported was pneumonia. How it came to this side effect is not clear. However, THC is said to lead to a to a higher risk of infections (Brown, 2020). The dronabinol prescribing information does not say anything about it though. Neither does the prescribing information of baclofen mention anything regarding infections as side effects (Ratiopharm GmbH, 2019).

3.5.4 Sedation

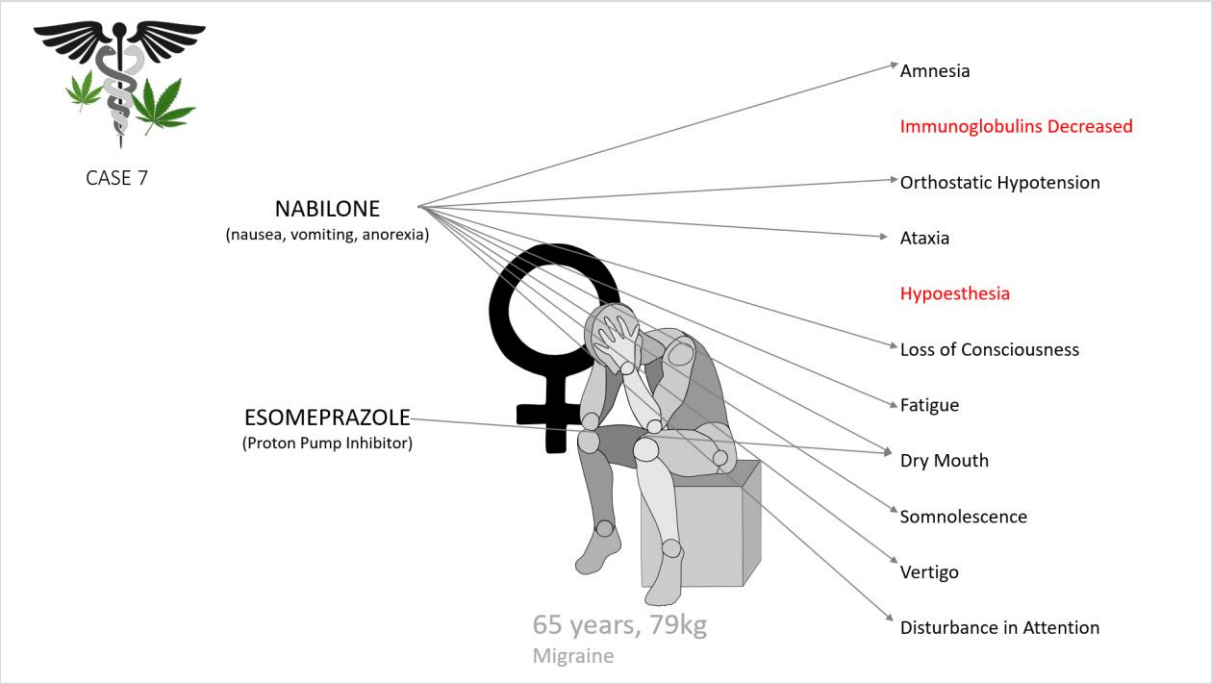


Figure 15. Case Report 7. *Presentation of the drugs taken and reported side effects.*

Case 7 (figure 15) describes a migraine patient, female, aged 65, who was under the therapy of two drugs: nabilone, which is indicated for nausea, vomiting and anorexia and esomeprazole, a proton pump inhibitor. Nabilone is not necessarily indicated for migraine patients, but is presumably used off-label, as migraine also often leads to side effects such as vomiting and nausea.The case was assigned to the sedation category because of occuring side effects like loss of consciousness, fatigue or somnolence. Most of the reactions might be caused by nabilone (Valeant Pharmaceuticals International, 2006), only 'dry mouth' is probably caused by esomeprazole, judged with the help of the prescribing information (AstraZeneca Pharmaceuticals, 2018). Nabilone might therefore be the main perpetrator. No clear explanation could be found for the reaction 'hypoaesthesia', the reduced sense of touch or sensation, and for 'immunoglobulins decreased'. The latter is probably caused by nabilone, since THC is said to increase the risk of infections. A physician should reconsider the use of esomeprazole, since migraine is listed as side effect, with a low frequency though (AstraZeneca Pharmaceuticals, 2018). Still, it is probably unsuitable for a migraine patient. In this case it can be seen very well how many side effects can be caused by a single cannabis preparation. The misconception that herbal preparations are free of side effects is clearly refuted here.

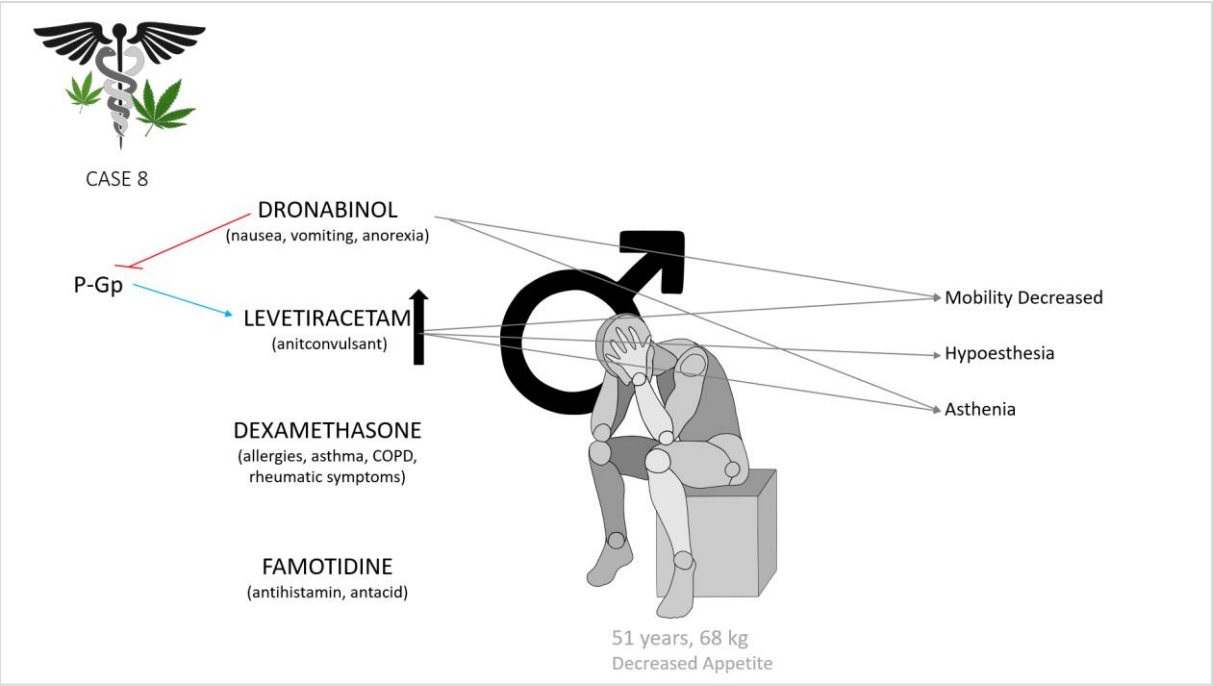


Figure 16. Case Report 8. *Presentation of the drugs taken and reported side effects.*

Case 8 (figure 16) describes a 51-year-old man who was on dronabinol therapy due to his decreased appetite, since it is indicated for anorexia, among other things. Besides that, he took levetiracetam, an anticonvulsant, dexamethasone, a corticosteroid and famotidine, an antihistamine. The side effects that occured, namely mobility decreased, hypoaesthesia and asthenia, were probably caused by both dronabinol and levetiracetam. Those two drugs might even interact with each other in a way that dronabinol inhibits P-Gp, which is responsible for the excretion of levetiracetam. This is followed by an increased concentration of levetiracetem. Dexamethasone and famotidine are of less relevance, although a change in preparation from famotidine should be considered. This is because the prescribing information of famotidine mentions decreased appetite as side effects, what the patient already suffers from (STADAPHARM, 2019). In summary, it can be said that dronabinol and levetiracetam presumably interact pharmacokinetically and pharmacodynamically.

3.5.5 More Extreme Age

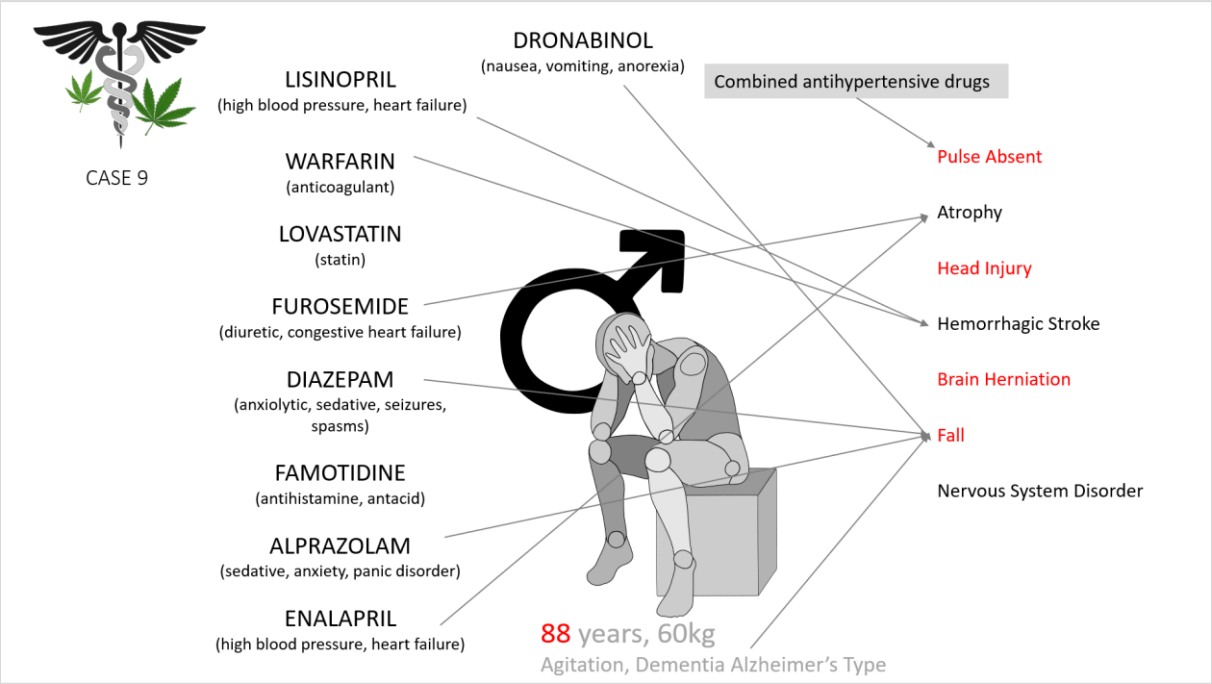


Figure 17. Case Report 9. *Presentation of the drugs taken and reported side effects.*

Case 9 (figure 17), an 88-year-old man suffering from agitation and Alzheimer's disease, took nine different drugs. Due to the relatively high, but almost average, number of drugs taken, the likelihood of interactions was very high. Drugs used against agitation are dronabinol, diazepam and alprazolam. The man also appeared to have cardiovascular problems since he is on lisinopril, warfarin, lovastatin, furosemide and enalapril therapy. He did not take any drugs against his diagnosed Alzheimer's disease though. Not only neuropsychiatric side effects, like nervous system disorder, were described, but also cardiovascular side effects such as stroke or absent pulse. Some side effects cannot be predicted with the help of already existing knowledge described in the prescribing information. These side effects include 'pulse absent', 'head injury', 'brain herniation' and 'fall'. However, when looking at the drug combinations, logical conclusions can be drawn. The absent pulse can probably be explained by the fact that various antihypertensive drugs are combined, which act synergistically. The combination might lead to an excessive blood pressure reduction followed by pulse absence. The other remaining reactions might have been caused by the nervous system disorder. It might have led to falls, which again might have let arised head injuries and, as a result, brain herniations. The latter could have also been caused by stroke. It was therefore a series of unfortunate events. The question is whether this could have been prevented? Since the patient already suffered from the neuropsychological disease Alzheimer's, this is difficult to

answer. In addition to the disease, dronabinol, diazepam and alprazolam also have an influence on this reaction. Far too many drugs work synergistically but in a negative way. In post-marketing studies of benzodiazepines falls and fractures have been observed. The risk was even higher if patients took additional sedatives and were older (Genentech, Inc., 2016). Lovastatin and warfarin increase the risk of bleeding, which in combination with benzodiazepines, might be extremely dangerous or even life-threatening (Bristol-Myers Squibb, 2019; Merck & Co., Inc., 2012). In addition to the synergistic effects already described, pharmacokinetic interactions are also possible, which makes the situation even worse. Warfarin and dronabinol both interact with CYP3A4, CYP2C9 and CYP1A2 as victim or/and perpetrator. This increases the concentration of both, warfarin and dronabinol (figure 18). The combination out of dronabinol and diazepam leads to a similar interaction, with the exception that the enzymes involved are CYP3A4 and CYP2C19 (figure 18). Dronabinol and alprazolam also behave similarly, but only interact via the enzyme CYP3A4 (figure 18)(Drugbank.com, 2020).

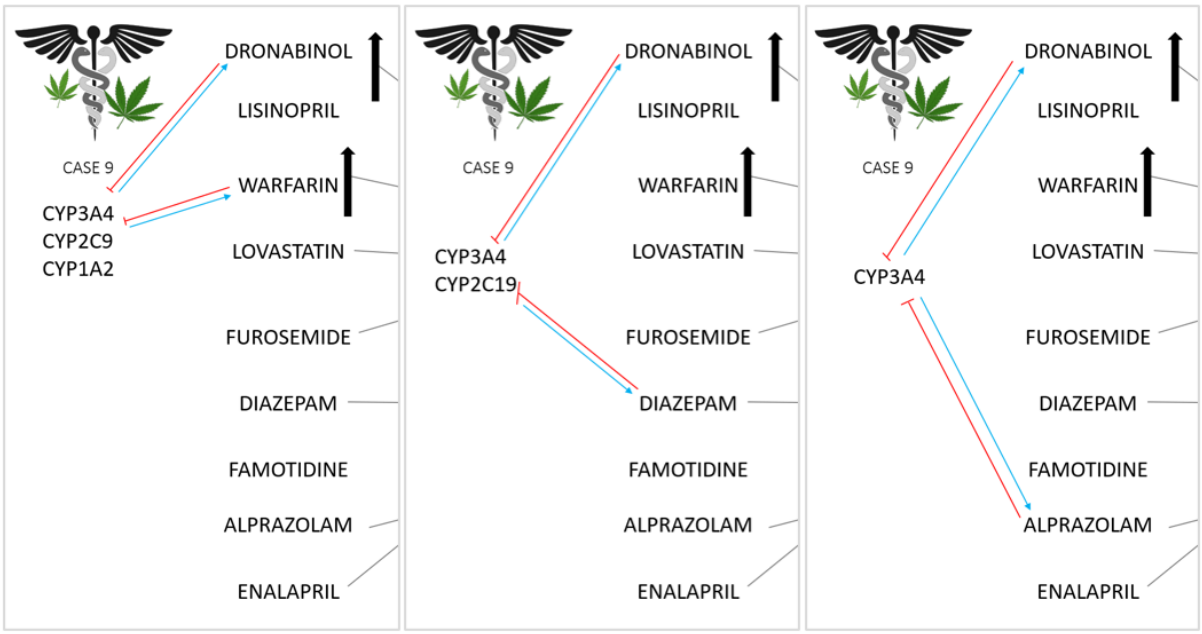


Figure 18. Case Report 9. *Presentation of relevant pharmacokinetic interactions and their influence of drug concentration.*

Since the full case narrative was not available, no statement could be made as to whether the listed drug combintions such as enalapril and lisinopril or diazepam and alprazolam were taken at the same time or over a certain period of time. Simultaneous use of these drugs should not be advocated. However, it is important to remember that some patients have prescriptions from different physicians, who do not even know that the patient has already received a

similar prescription. All in all, too many drugs have an impact on the neuropsychiatric system, including dronabinol. The result is excessive sedation with severe secondary reactions.

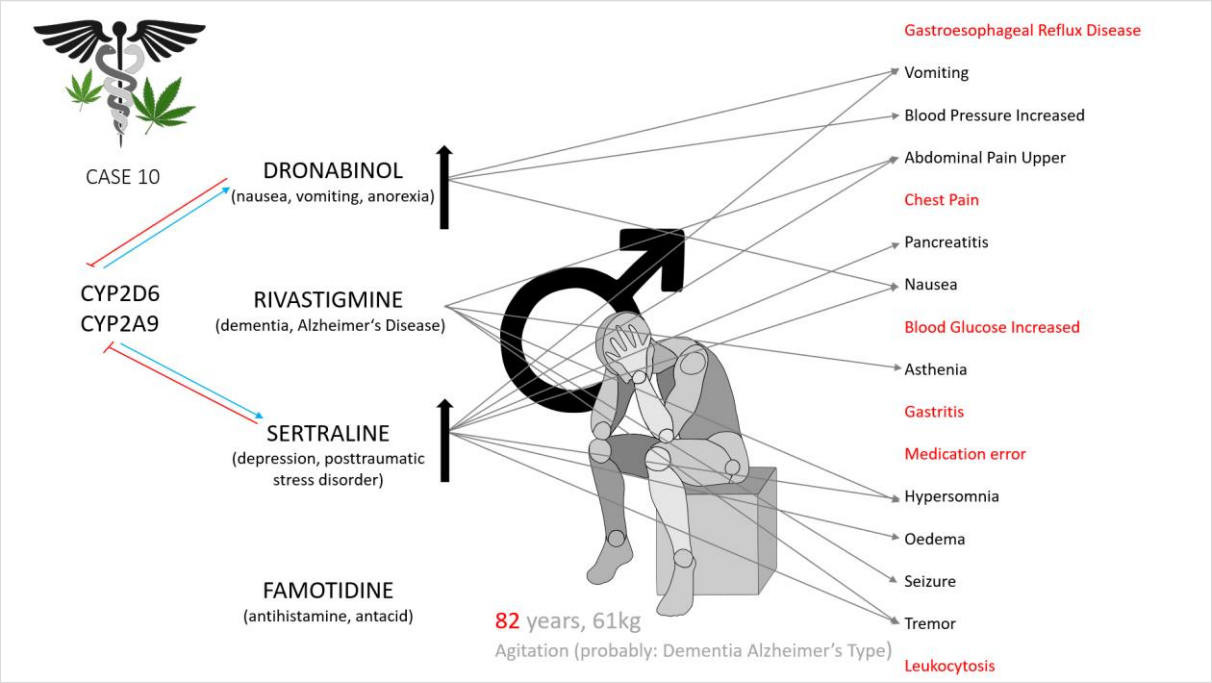


Figure 19. Case Report 10. *Presentation of the drugs taken and reported side effects.*

The next case (figure 19) is about an 82-year-old man who suffered from agitation. The drug therapy consisted of dronabinol, rivastigmine, which is indicated for dementia and Alzheimer's disease, sertraline, for depression and posttraumatic stress disorder and famotidine, an antihistamine. Reported were various reactions from each defined reaction class. These reactions are listed in figure 19. Most of these can be traced back to dronabinol, rivastigmine and sertraline (Lupin Pharmaceuticals, Inc., 2017; Novartis Pharmaceuticals Corporation, 2018; Patheon Softgels Inc., 2017). The following reactions cannot be explained on the basis of the prescribing informations: gastroesophageal reflux disease, increased blood glucose, gastritis, pallor, medication error and leukocytosis. Actually famotidine is indicated for GERD and gastritis so it is illogical why this patient still gets these reactions. One possible explanation is that the patient does not respond to famotidine and therefore should better change the drug. Reported leukocytosis makes even less sense, because both, sertraline and famotidine lead to leukopenia, which is exactly the opposite (Lupin Pharmaceuticals, Inc., 2017; STADAPHARM, 2019). As in several previous cases, pharmacokinetics also play an essential role. Dronabinol and sertraline are both interacting with CYP2D6 and CYP2A9 (Drugbank.com, 2020). They might act as substrate and as inhibitor as well, which is why the concentration of both drugs might increase. So not only pharmacodynamic but also pharmacokinetic

interactions are relevant. The remaining reactions, namely chest pain, increased blood glucose and pallor cannot be derived either.

In summary, there were some unclear and bizarre reactions mentioned in this case report. More information about the case is needed in order to be able to make reasonable statements.

3.5.6 Polypharmacy

Although polypharmacy is often defined by the use of at least five drugs (World Health Organization, 2019), the focus was on case reports with the highest number of drugs reported. The following cases were included.

Figure 20. Case Report 11. *Presentation of the drugs taken and reported side effects.*

Case 11 (figure 20) describes a 68-year-old woman with a wide variety of underlying diseases and symptoms. The number of drugs and nutritional supplements taken is 27, the one of reported side effects is 24.

Case 12 (figure 21), the last case report that has been chosen, is about a 52-year-old man suffering from anemia caused by a malignant disease. He took around 30 differend drugs and supplements and reported ten side effects.

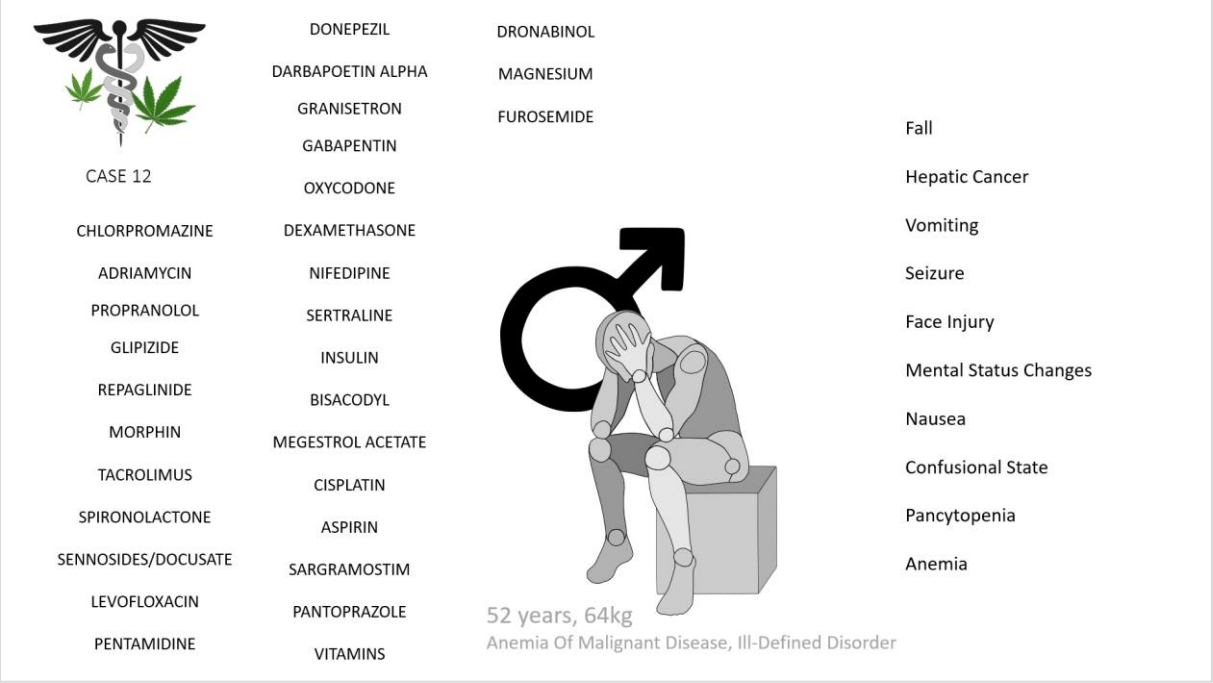


Figure 21. Case Report 12. *Presentation of the drugs taken and reported side effects.*

In both cases dronabinol was the prescribed cannabis ingredient, as it is often the case. Due to the huge amount of drugs and the wide range of possible interactions and side effects, it was not possible to analyse these cases without having detailed information on dosage, application type, co-diseases, patient history etc. In addition, it is unknown whether the reported drugs were taken at the same time or for a certain period of time before the event occured. In order to receive those information, a FOIA request needs to be made.

When searching for interesting case reports, those with a high number of drugs were automatically excluded because polymedication makes the analysis more difficult and less precise. Since polypharmacy is a big thing also with patients taking medical cannabis, the number of drugs in cannabis case reports have been counted (1,2,3,4,5,6,>6) and summarized in table 32.

Table 32. Number of Case Reports that Contain A Certain Number of Drugs.

# of drugs	All Cannabis Case Reports, ≥ 50 years	Prescribed Cannabis Case Reports, ≥ 50 years	Prescribed Cannabis Case Reports, < 50 years
1	19	0	0
2	135	105	92
3	127	53	62
4	96	49	96
5	132	32	135
6	102	30	105
>6	475	231	352

Number of people, that take 1, 2, 3, 4, 5, 6 or more than 6 drugs according to FAERS.

The reports were devided in people over 50 years consuming any kind of cannabis, people over 50 years taking medical cannabis and the ones under 50 years taking medical cannabis. There is hardly any difference when comparing the numbers in between the three subgroups. In all of them, however, it is clearly noticeable that the trend is towards six or more drugs.

4 Discussion

4.1 Trend and Comparison Between Age Groups

One of the main goals of this research was to find a trend in side effects associated with the use of medicinal cannabis in older adults. A statistical evaluation and calculation of PRR and ROR was not possible due to the unclean and incomplete database. Nevertheless, certain drugs are reported more frequently in combination with cannabis substances than others, which is a good hint for suspicious drug combinations. Since this work is not a clinical study, no statements can be made about existing interactions, but a trend in a certain direction is given. Frequently mentioned drugs are of particular interest when no interaction studies with cannabis exist. These drugs serve as guidelines for future medical cannabis interaction studies.

Differences of drug interaction patterns in between the different age groups can only be seen in the case reports with medically prescribed THC. This is because the majority of the CBD and nabiximols cases do not provide any information about age and therefore a comparison between young and old people is not possible. The created lists of ‘Interesting Drugs’ (table 35, 36 and 37) include those substances that have been reported more frequently in older patients in combination with cannabis and where no interaction is known yet. Drugs that are generally prescribed more frequently in older people are of less interest. For example, rivastigmine, a drug which is indicated in Alzheimer's disease, is reported more frequently in older patients. Due to the physiological and well-known course of the disease, this disease mostly affects older peopler. It means that the cause of the frequent reports in older adults does not necessarily stand for a more frequent occurrence of side effects but rather for a increased prescription rate in old people.

FAERS case reports containing any cannabis product do not state whether cannabis was used medicinally or recreationally. A medical use is assumed if the preparation has been approved by the FDA or EMA and needs a medical prescription. A total of 1,072 cases were reported in people over 50 years of age, 500 of those can be assigned to medical use. 4,186 cases were found among people under 50 years of age. Of these, only 847 cases can be assigned to medical use (see chapter 2.4.1-2.4.2). The remaining cases do not provide any reason for use, so recreational use is assumed. This is also because the latter reports mention terms like ‘drug abuse’, ‘drug addiction’, ‘intentional drug misuse’ or ‘overdose’. Younger people generally tend to consume more cannabis, although there is a trend towards older people (Han et al.,

2017). It has also been observed that people under 50 years, suspected of taking cannabis medicinally, often take addictive drugs in combination. Possibly these synthetic THC analoga (dronabinol, nabilone), which lead to hallucinogenic effects, are misused by those people.

In addition to drug-drug interactions, drug-disease interactions were also of interest. It soon became clear that this analysis requires case narratives which show the patient's medical history and co-diseases. Although the patient's illness sometimes is mentioned in the 'Reason for Use' column, it is missing often. This is mainly confirmed by the fact that the prevalence of the illness in the population compared to the prevalence mentioned in the case reports is a lot higher. To a certain extent it is possible to draw conclusions about the disease from the patients' medication. However, many drugs are indicated for various diseases, which leads to very uncertain and vague statements.

When looking at the individual case reports, no real trends were found, but one can say that pharmacokinetic and synergistic pharmacodynamic interactions are in balance. There are some side effects or reactions where no cause could be deduced. This is partly due to the lack of information in the database. However, these could also be side effects of cannabis or interactions with cannabis that are not known yet.

4.2 Strengths

4.2.1 In General

In this thesis, various calculations were made to clearly show the frequencies and distributions of reported side effects with cannabis products. This descriptive analysis gives an overview of the current situation regarding medical cannabis use. The focus is on the older population, as they often take many additional drugs, have an altered metabolism and are excluded in clinical studies. Older people also tend to use medicinal cannabis more than younger people, who use cannabis rather recreationally. In addition, a wide variety of tables were created with information on side effects, interactions and frequencies of concomitant drugs that were mentioned. These are based on the current state of research and were carried out with a good conscience. The tables enable to draw conclusions about a trend in a certain direction.

Data from this thesis serve as guideline for future interaction studies with cannabis. Drugs that do not even appear in the cannabis case reports could actually be excluded from further interaction studies because since 1968 (foundation of FAERS) no other drugs have been

reported in combination with cannabis than the drugs already mentioned in the 'Table of Drugs'.

4.2.2 FAERS-Database

The FDA Adverse Event Reporting System is a widely used database, which is publicly available and serves as support for post-marketing surveillance programs (Hoffman et al., 2014). FAERS is a spontaneous reporting system for side effects occurring worldwide. It is extremely helpful with monitoring side effects of already approved drugs. Side effects very often do not occur in clinical studies because, among other things, not all population groups can be tested. If any safety signal occurs it might be necessary to take the suspected drug off the market in order to ensure no further incidents.

Another strength is that it includes a broad patient population, like elderly, children, people with specific co-morbidities etc. This is particularly important for this thesis, because the focus lies on the comparison of side effects in older and younger cannabis users. Since FAERS receives reports either from the consumer itself, the healthcare provider or pharmaceutical company the reports cover a wide range of really occurring cases. This is because all people involved in the health system are obliged to report any side effect that occurs. It follows that even rare events are reported, which is also a great benefit of FAERS.

An additional positive aspect of the database is, that it is possible to find reporting trends in the database. These can be analyzed as it was done in this thesis (U.S. Food and Drug Administration, 2016). As far as we know, the FAERS database has not been used for cannabis research yet, which is why it served as the data source of choice despite its many limitations.

4.3 Limitations

4.3.1 In General

This research thesis also has some limitations. First, the statistical metrics ROR and PRR were not calculated, unlike originally planned. These calculations would show whether a certain cannabis preparation is often associated with certain side effects and how strong this association is in comparison to a positive and negative control group. Since there are a total of 963 reactions in the cannabis case reports, all of them might represent a drug that potentially interacts with cannabis. Therefore the calculation of ROR and PRR would need to be done for each cannabis preparation in combination with each reported side effect. This is

time-consuming but possible though. However, it is still problematic, because many reactions are similar but not the same. For example, reactions such as 'blood pressure abnormal', 'blood pressure increased' or 'blood pressure systolic increased' could be the same reaction differently described. One approach would be to summarize these similar side effects in order to make clear statements about occuring reactions. Unfortunately, it is also not possible to simply add up the frequencies since a single case report often contains several similar terms. This would end up in even more duplicates than already exist in the original database. As a recommendation for future studies, researchers could focus on certain side effects and choose a positive and negative control, in order to calculate ROR and PRR. However, this was not our research question.

Second, there are a lot of missing data, especially when it comes to age. CBD and nabiximols case reports often do not contain any information about how old the person was or still is. It was therefore not possible to make any statements on age-specific side effects or interactions, as was actually one focus of the thesis. In addition, there was a lack of data in the analysis of pharmacokinetic interactions, since the binding to plasma proteins or receptors was not investigated at all.

Third, small parts of the thesis were judged relatively subjectively. For example, the assessment of which side effect category a case report belongs to or if it belongs to any is subjective and difficult to make. To counteract that, Lea Gnatzy, a German pharmacy student who also conducted research at the UF helped with that research step as part of her practical year. Based on the four-eye-principle, conclusions were drawn together. Case reports that could not be assigned to a specific reaction class were placed in group five, which contain all unclassified cases.

Fourth, only older people with a certain disease (e.g. cancer, multiple sclerosis, etc.) were included in the analysis. This is because the focus was on medically prescribed cannabis, which is only indicated for certain diseases. Healthy old people who usually do not consume medical cannabis are of course not taken into account here. However, it can be assumed that the tolerability is even better with healthy people than with people who are already ill.

Sixth, full case narratives are not available, which is probably one of the strongest restrictions. As already mentioned, no FOIA request in order to obtain full case reports could be carried out. This request should be made at the beginning of the work, since it may take months

before this request is processed and finally available. However, you have to give precise details on your request, like for example which report you are interested in. Since it took around four months to find out which drugs and finally case reports would be interesting for a closer analysis, it was too late for a FOIA request. Due to Corona, it would have been delayed even more. This limitation made a closer analysis of cannabis interactions with certain diseases impossible, but might be a question for future research.

4.3.2 FAERS

There exist several limitations in FAERS. First, the cause of the reported reactions is not clear (U.S. Food and Drug Administration, 2018). It can either be a side effect of a single drug, a drug-drug interaction, or a drug-disease interaction. The possibilities are diverse. In addition, incorrect conclusions can often be drawn. For example, if a drug is used to treat serious mental disorders, death cannot be simply considered as an extreme severe adverse event, since affected patients are under a certain risk of suicide related death. Therefore, a good professional analysis is necessary to rule out incorrect conclusions.

Second, since people in the healthcare sector are obliged to report side effects, it happens quite often that the same side effect is reported multiple times and therefore duplicates exist. (U.S. Food and Drug Administration, 2018) These duplicates are not always easy to recognize because the data, e.g. date, concomitant drugs, reason for use etc. differ minimally from one another. Figure 22 gives an example of duplicates that are mostly congruent, but still have deviations.

A	B	C	D	E	F	G	H	I	J	K	L	M
Case ID	Suspect Product N	Suspect Pro	Reason for	Reactions	Serious	Outcomes	Sex	Event Date	Latest FDA F	Case Priorit	Patient Age	Patient Wei
16731973	Enbrel;Ativan;Cesam	Duloxetine Hy	Ankylosing Sp	Mood Altered	Serious	Other Outcon	Female	-	06-JAN-2020	Expedited	50 YR	79 KG
16416694	Cymbalta;Enbrel;Ces	Lorazepam;Na	Ankylosing Sp	Mood Altered	Serious	Other Outcon	Female	-	06-JAN-2020	Expedited	50 YR	79 KG
16357404	Enbrel;Cesamet;Cym	Lorazepam;Pa	Ankylosing Sp	Sacroiliitis;Mc	Serious	Other Outcon	Female	-	06-JAN-2020	Expedited	50 YR	79 KG
14551434	Cymbalta;Ativan;Ces	Etanercept;Pa	Ankylosing Sp	Fatigue;Fibror	Serious	Other Outcon	Female	-	03-JAN-2020	Expedited	50 YR	79 KG
16385097	Cesamet;Ativan;Cym	Etanercept;Tr	Ankylosing Sp	Somatic Symp	Serious	Other Outcon	Female	-	31-DEC-2019	Expedited	50 YR	79 KG
14014687	Enbrel;Ativan;Cesam	Duloxetine Hy	Ankylosing Sp	Drug Ineffecti	Serious	Other Outcon	Female	-	31-DEC-2019	Expedited	50 YR	79 KG
17140763	Enbrel;Cesamet;Cym	Lorazepam;Ar	Ankylosing Sp	Sacroiliitis;Th	Serious	Other Outcon	Female	-	23-DEC-2019	Non-Expedite	50 YR	79 KG
17002221	Ativan;Cymbalta;Enb	Etanercept;Na	Ankylosing Sp	Drug Ineffecti	Serious	Other Outcon	Female	-	17-DEC-2019	Expedited	50 YR	79 KG
17001840	Cymbalta;Enbrel;Ativ	Lorazepam;Et	Product Used	Somatic Symp	Serious	Other Outcon	Female	-	16-DEC-2019	Expedited	50 YR	79 KG
16971254	Cymbalta;Enbrel;Ativ	Nabilone;Lora	Ankylosing Sp	Fibromyalgia;	Serious	Other Outcon	Female	-	10-DEC-2019	Expedited	50 YR	79 KG
15927778	Ativan;Enbrel;Cymba	Duloxetine Hy	Ankylosing Sp	Therapeutic P	Serious	Other Outcon	Female	-	09-DEC-2019	Expedited	50 YR	79 KG
14488119	Enbrel;Ativan;Cymba	Nabilone;Quir	Ankylosing Sp	Sleep Disorde	Serious	Other Outcon	Female	-	04-DEC-2019	Expedited	50 YR	79 KG
16340551	Fentanyl Transderma	Fentanyl;Ibup	Fibromyalgia;	Therapeutic P	Serious	Hospitalized;(	Male	-	26-NOV-2019	Expedited	59 YR	Not Specified
16211363	Cesamet;Cymbalta;E	Lorazepam;Pa	Ankylosing Sp	Fatigue;Sleep	Serious	Other Outcon	Female	-	26-NOV-2019	Expedited	50 YR	79 KG
16881163	Ativan;Cesamet;Enbr	Duloxetine Hy	Ankylosing Sp	Fibromyalgia;	Serious	Other Outcon	Female	-	25-NOV-2019	Expedited	50 YR	79 KG
16258361	Cesamet;Ativan;Cym	Etanercept;Tr	Ankylosing Sp	Sacroiliitis;Co	Serious	Other Outcon	Female	-	20-NOV-2019	Expedited	50 YR	79 KG

Figure 22. Example of Duplicates. *Data in between the reported cases are similar but do not provide identical information. This makes it hard to delete case reports which are mentioned several times.*

In future studies it would probably make sense to develop a kind of formula that records case reports as duplicates as soon as, for example, 80% of the content is the same. These duplicates can then be removed very easily, which subsequently makes statistical calculations possible.

Third, there are a great amount of incomplete reports (U.S. Food and Drug Administration, n.d.). Very often there is no information on age or gender. Also, it cannot be assumed that the list of taken drugs is complete. Missing data often makes it hard to properly evaluate an event.

Fourth, information provided has not been verified (U.S. Food and Drug Administration, n.d.).

Fifth, rates of occurrence cannot be calculated with this data base (U.S. Food and Drug Administration, n.d.). It can only give hints for presumably interacting drugs. Clinical studies are indespensable.

Sixth, the FAERS dashboard does not disclose any information about the application method, comorbidities and dosage of drugs administered. This information can only be found in the full case reports, which can be requested after paying a certain fee.

Seventh, pharmacogenetics also is not included in the FAERS data. However, pharmacogenetics is becoming more and more relevant because it has a large impact on the enzyme equipment and, as a result, the tolerability of drugs. The question is also, how many physicians test their patients for polymorphisms at all.

Eighth, as in every other pharmacovigilance database, reporting bias also plays a major role. On the one hand, people forget to report all information about their previous drug history, consumption of alcohol or cigarettes, etc. The report is therefore not complete. On the other hand, the data might also influence the reporting patterns of consumers, since the database is publicly available and all previously reported cases regarding a specific drug can be viewed very easily. This can cause a so-called nocebo effect in the patient.

4.3.3 AEOLUS

In order to simplify the process of cleaning data and removing duplicates in FAERS, there is the option of using an already cleaned database. Some refurbished databases exist, which are usally accessable for a fee. However, there is also a publicly accessible curated and standardized adverse drug event resource called AEOLUS.

AEOLUS, Adverse Event Open Learning through Universal Standardization, is based on FAERS. It does not contain any duplicates, but has standardized vocabulary of drugs and outcomes. It

also provides statistics about drug-outcome relationships. This database can be easily downloaded online via the Dryad website, in order to carry out individual analysis (Banda et al., 2016).

AEOLUS has already been mentioned a few times in literature. For example, in a study about suicide-related adverse events, researchers have made use of this database for their research (Ding & Chen).

Why this purified database was not used for this thesis is easy to explain. AEOLUS only contains case reports from January 2004 to June 2015, which means that the increasing number of cannabis-related cases in the last years is completely excluded. The database is therefore not up to date. Furthermore, AEOLUS does not take demographic information into account. This means that FAERS would have to be used in addition anyway to obtain the demographic data of patients, like sex or age, which is particularly relevant in order to be able to determine age-specific side effects.

5 Conclusion

5.1 Safety and Efficacy of Cannabis Products

This research does not allow any statements to be made regarding the safety or efficacy of cannabis in medical use. Pharmacovigilance systems, like FAERS, can only detect safety signals, which must be examined in more detail in clinical studies in order to make reliable statements. Drugs that could be of interest for future studies are summarized in chapter 5.2.

A prospective uncontrolled cohort study that dealt with the efficacy and safety of medicinal CBD in older people needs to be mentioned. It describes the effects of medical cannabis in around 2,700 patients of over 65 years of age. Cannabis was taken for various reasons. It turned out, that the use of cannabis is safe in older people. However, this study was carried out by using a questionnaire. There was neither a control group nor a randomization, which is why no information about the efficacy of the treatment can be obtained from this study. The level of evidence is therefore relatively low (Abuhasira et al., 2018).

5.2 Potential for Interactions with Cannabis

The following are lists of drugs that could potentially lead to interactions in older people when being combined with CBD, THC or nabiximols. Drugs that could be of interest in interaction studies with CBD are ascorbic acid, vitamin D, calcium, clonidine, fluticasone, folic acid, levothyroxine, melatonin, montelukast, omeprazole, oxcarbazepine, phenytoin, polyethylene glycol, ranitidine, risperidone.

This list of interesting drugs is longer for THC: Ampicillin, aspirin, benperidol, cisplatin, citric acid, cyclophosphamide, darbapoetin alfa, dexamethasone, esomeprazole, etoposide, famotidine, fludrocortisone, glipizide, granisetron, levetiracetam, levothyroxopine, magnesium, metamizole, predothyroxopine, magnesium, metamizole, metetramidine, pantetramidine, quetramidin sargramostim, sodium bicarbonate, sodium chloride, sulbactam, trimethoprim, vemurafenib, zuclopenthixol, atorvastatin, bromazepam, flupentixol, lorazepam, pipamperone, quetiapine, spironolactone, tacrolimus, dexamethasone, clozaprazole, omeprazole.

The following drugs are suggested to examine in interaction studies with nabiximols: Acetaminophen, baclofen, dalfampridine, human interferon beta, methylprednisolone, ocrelizumab, pantoprazole.

When looking at the case reports in FAERS that contain medical cannabis and patients with at least 50 years of age, the following side effects can be observed. 29.6% of the side effects are of neuropsychiatric origin, 5.4% of cardiovascular origin, 5.4% of the side effects are related to infections of any kind and 2.4% related to sedation.

A literature review from 2003 describes, that a lot of side effects can be prevented if being aware of them (Kanjanarat et al., 2003). These side effects are analyzed in detail without reference to cannabis. It was found that the median preventability rate of adverse events in hospitals was 35.2%. Most of them occurred in the prescribing stage and were dose-related. Drugs that were very often associated with preventable side effects were antihypertensive drugs such as beta blockers, ACE inhibitors and nitrates, centrally acting substances such as sedatives, antidepressants and benzodiazepines, analgesics such as opioids and anti-infectives such as penicillins and cephalosporins. This is an interesting finding, since CBD and THC often might be combined or taken instead of the before-mentioned drugs. To what extent it is advantageous to replace the drugs with cannabis (e.g. opioids, sedatives) or combine it with cannabis (e.g. antihypertensives, antidepressants) still requires a good benefit-risk assessment of drug therapy. Ongoing drug monitoring and dose titration are very important when administering cannabis, as the number of studies is still very limited, especially for older patients.

5.3 Need for Research and Perspectives

The FAERS database is a good basis for giving an overview and showing trends of possible reactions. Still, it does not allow any reliable statements about side effects or interactions of cannabis in older people. This is only possible through clinical studies. Although medical cannabis is an increasingly important topic, especially among older adults, there are hardly any interaction studies with cannabis and other drugs. Also, the few studies that exist were carried out in young rather than old people. The older population in particular should be tested for interactions with medicinal cannabis, as those are known to take more drugs that potentially interact with the cannabis product. In addition, old people have different metabolic conditions.

As described in a paper about the safety and benefits of CBD (Iffland & Grotenhermen, 2017), a number of research questions are still open in future, like how CBD affects a larger number of patients over a longer period of time or if it has an impact on the hormone status or the genes. These and many more questions can of course also be questioned about THC. It is therefore an urgent matter to investigate the safety of medical cannabis more closely, especially in older adults, in order to eliminate uncertainties regarding its application that exists due to the lack of studies. Until then, pharmacists and their pharmaceutical knowledge and skills are indispensable when it comes to dosing, side effects and interactions. Pharmacists also play an important role in educating patients for ensuring the safe use of medical cannabis. In cases where drug-drug interactions are not known and therefore unavoidable, clear clinical guidance must be provided, such as start low and go slow. If possible interactions are already suspected, an alternative preparation should be selected.

A goal of all healthcare providers should be to advocate progress in the research of medical cannabis in order to clear up ambiguities and uncover unknown interactions (Schmitz & Richert, 2020). In particular, the risk-benefit ratio of medical cannabis (e.g. CBD) for indications outside those approved by the FDA or EMA can only be assessed if, in addition to safety, also its benefits is demonstrated in prospective, randomized, controlled clinical trials.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AEOLUS	Adverse Event Open Learning through Universal Standardization
AIDS	Acquired Immune Deficiency Syndrome
BCRP	Breast Cancer Resistance Protein
BSEP	Bile Salt Export Pump
CB1	Cannabinoid Receptor 1
CB2	Cannabinoid Receptor 2
CBD	Cannabidiol
CB(s)	Cannabinoids
CES1	Carboxylesterase 1
CINV	Chemotherapy-induced Nausea and Vomiting
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P450
e.g.	example given
FABP	Fatty Acid Binding Protein
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Terms
HLT	High Level Terms
LLT	Lowest Level Terms
MedDRA	Medical Dictionary for Regulatory Activities
MRP1	Multidrug Resistance Protein 1
OTC	over the counter
PD	Pharmacodynamic
P-Gp	P-Glycoprotein
PK	Pharmacokinetic
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio

PT	Preferred Terms
SOC	System Organ Classes
subsp.	subspezies
THC	Delta-9-tetrahydrocannabinol
THC-COOH	Tetrahydrocannabinolic Acid
TRPV1	Transient Receptor Potential Vanilloid Type 1
UGT	Uridine-5’-diphospho-glucoronosyltransferase
UF	University of Florida
U.S.	United States
USA	United States of America
VDAC1	Voltage Dependent Anion Channel 1
WHO	World Health Organization
5-HT	5-Hydroxytryptamine
7-COOH-CBD	7-Carboxycannabidiol
#	Number

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Appendix

Table 33. 'Pharmacokinetic Interactions'. *Presumable pharmacokinetic interactions between cannabis ingredients and any other drug, which has been mentioned in the 'Table of Drugs'. No = presumably no pharmacokinetic interaction with CBD/THC/nabiximols because drug and CBD/THC/nabiximols interact with different enzymes/transporters; yes = presumably pharmacokinetic interaction in between drug and CBD/THC/nabiximols; - no information available; Nabix. = nabiximols; 0 = no substrate (when in victim column) or no inductor/inhibitor (when in perpetrator column); 1 = substrate; 2 = inductor; 3 = inhibitor; 4 = downregulator; * = possible interaction*

Presumable PK-Interactions between	CBD	as Victim	as Perpetrator	THC	as Victim	as Perpetrator	Nabix.	as Victim	as Perpetrator
Abatacept	no	0	0	no	0	0	no	0	0
Acetaminophen	yes	1	3	yes	1	2,3	yes	1	2
Acetylcysteine	no	0	0	no	0	0	no	0	0
Acyclovir	yes	1*	3*	yes	1*	3*	yes	1*	3*
Adalimumab	no	0	0	no	0	0	no	0	0
Alendronic Acid	no	0	0	no	0	0	no	0	0
Alfuzosin	yes	1*	3	yes	1*	3	yes	1*	3
Alimemazine	no	0	0	no	0	0	no	0	0
Alizapride	no	0	0	no	0	0	no	0	0
Allopurinol	no	0	0	no	0	0	no	0	0
Alprazolam	yes	1*	3	yes	1*	2,3	yes	1	3
Amantadine	no	0	0	no	0	0	no	0	0
Aminosalicylic Acid	no	0	0	no	0	0	no	0	0
Amiodarone	yes	1	3	yes	1	2,3	yes	1	3
Amisulpride	no	0	0	no	0	0	no	0	0
Amitriptyline	yes	1	3	yes	1*	2,3	yes	1	3
Amlodipine	yes	1	3	yes	1*	2,3	yes	1	3
Amoxapine	yes	1	3	yes	1*	3	yes	1	3
Amoxicillin	no	0	0	no	0	0	no	0	0
Amphetamine	yes	1*	3	yes	1*	3	yes	1*	3
Ampicillin	no	0	0	no	0	0	no	0	0
Anakinra	no	0	0	no	0	0	no	0	0
Apixaban	yes	1*	3	yes	1*	2,3	yes	1*	3
Apremilast	yes	1*	3	yes	1*	3	yes	1*	3
Aprepitant	yes	1	3	yes	1	2,3	yes	1	3
Aripiprazole	yes	1*	3	yes	1*	3	yes	1*	3
Armodafinil	yes	1	3*	yes	1	2*,3*	yes	1	3*
Arnica Montana Flower	-	-	-	-	-	-	-	-	-
Ascorbic Acid	no	0	0	no	0	0	no	0	0
Aspirin	yes	1	3	yes	1*	2,3	yes	1	3*
Atenolol	yes	1*	3	yes	0	3	yes	1*	3
Atorvastatin	yes	1	3	yes	1	2*,3	yes	1	3
Atropine	yes	0	3	no	0	0	no	0	0
Avelumab	no	0	0	no	0	0	no	0	0

Azithromycin	yes	1	3	yes	1	3	no	1	3
Baclofen	no	0	0	no	0	0	no	0	0
Beclomethasone Dipropionate	yes	1	3	yes	1	3	yes	1	3
Benazepril	no	0	0	no	0	0	no	0	0
Benperidol	-	-	-	-	-	-	-	-	-
Benzatropine	no	0	0	no	0	0	no	0	0
Benzodiazepine	yes	1*	3	yes	1*	3	yes	1*	3
Benzoylecgonine	no	0	0	no	0	0	no	0	0
Bevacizumab	no	0	0	no	0	0	no	0	0
Bictegravir	yes	1*	3	yes	1*	3	yes	1*	3
Biotin	yes	1*	3*	yes	1*	3*	yes	1*	3*
Bisacodyl	no	0	0	no	0	0	no	0	0
Bisoprolol	yes	1*	3*	yes	1*	3*	yes	1*	3*
Bleomycin	no	0	0	no	0	0	no	0	0
Boceprevir	yes	1	3	yes	1	3	yes	1	3
Bosentan	yes	1	3	yes	1	2,3	yes	1	3
Brimonidine	no	0	0	no	0	0	no	0	0
Brinzolamide	yes	1*	3	yes	1*	3	yes	1*	3
Brivanib Alaninate	-	-	-	-	-	-	-	-	-
Brivaracetam	yes	1*	3	yes	1*	2,3	yes	1*	3
Bromazepam	yes	1*	3	yes	0	3	yes	1*	3
Budesonide	yes	1	3	yes	1	3	yes	1	3
Bumetanide	no	0	0	no	0	0	no	0	0
Bupivacaine	yes	1*	3	yes	1*	3	yes	1*	3
Buprenorphine	yes	1	3	yes	1	2,3	yes	1	3
Bupropion	yes	1	3	yes	0	2,3	yes	1	3*
Buspirone	yes	1*	3	yes	1*	3	yes	1*	3
Butalbital	no	0	0	no	0	0	no	0	0
Caffeine	yes	1*	3	yes	1*	2,3	yes	1*	3
Calcium	no	0	0	no	0	0	no	0	0
Calcium Carbonate	no	0	0	no	0	0	no	0	0
Calcium Chloride	no	0	0	no	0	0	no	0	0
Calcium Phosphate	no	0	0	no	0	0	no	0	0
Canakinumab	no	0	0	no	0	0	no	0	0
Candesartan	yes	1	3	yes	1	2,3*	yes	1	0
Carbamazepine	yes	1	3	yes	1	2*,3	yes	1	3
Carbazochrome	no	0	0	no	0	0	no	0	0
Carbidopa	no	0	0	no	0	0	no	0	0
Carboplatin	no	0	0	no	0	0	no	0	0
Carboxymethyl-cellulose	no	0	0	no	0	0	no	0	0
Cariprazine	yes	1*	3	yes	1*	3	yes	1*	3
Carisoprodol	yes	1*	3	yes	0	3	yes	1*	3

Carvedilol	yes	1*	3	yes	1*	2,3	yes	1*	3
Cefaclor	yes	0	3	no	0	0	no	0	0
Cefepime	no	0	0	no	0	0	no	0	0
Ceftriaxone	yes	0	3*	yes	0	3*	no	0	0
Cefuroxime	no	0	0	no	0	0	no	0	0
Celecoxib	yes	1	3	yes	1*	2,3	yes	1	3
Cephalexin	no	0	0	no	0	0	no	0	0
Cetirizin	yes	1*	3	yes	1*	3	no	0	0
Cetuximab	no	0	0	no	0	0	no	0	0
Chlordiazepoxide	yes	1*	3	yes	1*	3	yes	1*	3
Chlorpromazine	yes	1	3	yes	1	3	yes	1	3
Chlorthalidone	no	0	0	no	0	0	no	0	0
Cholecalciferol	yes	1*	3	yes	1*	3	yes	1*	3
Cholestyramine	no	0	0	no	0	0	no	0	0
Chondroitin Sulfate	no	0	0	no	0	0	no	0	0
Cilostazol	yes	1*	3	yes	1*	3	yes	1*	3
Ciprofloxacin	yes	1	3	yes	1	3	yes	1	3*
Cisplatin	yes	1	3	yes	1	3	yes	1	3*
Citalopram	yes	1	3	yes	1	3	yes	1	3
Citicoline	-	-	-	-	-	-	-	-	-
Citric Acid	no	0	0	no	0	0	no	0	0
Clavulanic Acid	no	0	0	no	0	0	no	0	0
Clindamycin	yes	1	3	yes	1	3	yes	1	3
Clobetasol	yes	1	3	yes	1	3	yes	1	3
Clobetasol Propionate	yes	1	3	yes	1	3	yes	1	3
Clonazepam	yes	1*	3	yes	1*	3	yes	1*	3
Clonidine	yes	1*	3	yes	1*	2,3	yes	1*	3
Clopidogrel	yes	1	3	yes	1	2,3	yes	1	3
Clotrimazole	yes	1	3	yes	1	2*,3	yes	1	3
Clozapine	yes	1	3	yes	1	2,3	yes	1	3
Cobalamin	-	-	-	-	-	-	-	-	-
Cobimetinib	yes	1*	3	yes	1*	3	yes	1*	3
Cocaine	yes	1	3	yes	1*	3	yes	1	3
Codeine	yes	1*	3	yes	1*	3	yes	1*	3
Colchicine	yes	1	3	yes	1	3	yes	1	3
Colestipol	no	0	0	no	0	0	no	0	0
Collagen	-	-	-	-	-	-	-	-	-
Conjugated Estrogens	yes	1*	3	yes	1*	3	yes	1*	3
Corticotropin	yes	1	3	yes	1	3	yes	1	3
Cortisone Acetate	yes	1	3	yes	1	3	yes	1	3
Crizotinib	yes	1	3	yes	1	3	yes	1	3
Curcumin	yes	1	3*	yes	1	2*,3*	yes	1	3*

Cyclizine	yes	1	3*	yes	1	2*	yes	1	0
Cyclobenzaprine	yes	1*	3	yes	1*	3	yes	1*	3
Cyclophosphamide	yes	1	3	yes	1	2,3	yes	1	3
Cyclosporine	yes	1	3	yes	1	3	yes	1	3
Dabigatran Etexilate	yes	0	3	yes	0	3	no	0	0
Daclatasvir	yes	1*	3	yes	1*	3	yes	1*	3
Dalfampridine	no	0	0	no	0	0	no	0	0
Dantrolene	no	0	0	no	0	0	no	0	0
Danvatirsen	-	-	-	-	-	-	-	-	-
Daprodustat	no	0	0	no	0	0	no	0	0
Darbepoetin Alfa	no	0	0	no	0	0	no	0	0
Darunavir	yes	1	3	yes	1	3	yes	1	3
Dasabuvir	yes	1*	3	yes	1*	3	yes	1*	3
Dasatinib	yes	1	3	yes	1	2,3	yes	1	3
Deflazacort	yes	1	3	yes	1	3	yes	1	3
Denosumab	no	0	0	no	0	0	no	0	0
Desloratadine	yes	1*	3*	yes	1*	3*	no	0	0
Desmopressin	no	0	0	no	0	0	no	0	0
Desvenlafaxine	yes	1	3	yes	1	3	yes	1	3
Dexamethasone	yes	1	3	yes	1	2*,3	yes	1	3
Dextro-amphetamine	yes	1*	3	yes	0	3	yes	1*	3
Dextro-methorphan	yes	1*	3	yes	1*	2,3	yes	1*	3
Dextro-propoxyphene	yes	1	3	yes	1	3	yes	1	3
Diamorphine	yes	0	3	yes	0	3	no	0	0
Diazepam	yes	1	3	yes	1	2,3	yes	1	3
Diclofenac	yes	1	3	yes	1	2,3	yes	1	3
Dicyclomine	no	0	0	no	0	0	no	0	0
Digoxin	yes	1*	3	yes	1*	3	no	0	0
Dihydrocodeine	yes	1*	3	yes	1*	3	yes	1*	3
Diltiazem	yes	1	3	yes	1	3	yes	1	3
Dimenhydrinate	no	0	0	no	0	0	no	0	0
Diosmin	no	0	0	no	0	0	no	0	0
Diphenhydramine	yes	1	3	yes	1*	2,3	yes	1	3
Diphenoxylate	no	0	0	no	0	0	no	0	0
Docusate	no	0	0	no	0	0	no	0	0
Dofetilide	yes	1*	3	yes	1*	3	yes	1*	3
Domperidone	yes	1*	3	yes	1*	3	yes	1*	3
Donepezil	yes	1*	3	yes	1*	2,3	yes	1*	3
Dopamine	no	0	0	no	0	0	no	0	0
Dorzolamide	yes	1*	3	yes	1*	2	yes	1*	0
Doxazosin	yes	1*	3	yes	1*	2,3	yes	1	3

Doxepin	yes	1	3	yes	1*	2,3	yes	1	3
Doxorubicin	yes	1	3	yes	1	3	yes	1	3
Doxycycline	yes	1	3	yes	1	3	yes	1	3
Droperidol	no	0	0	no	0	0	no	0	0
Duloxetine	yes	1	3	yes	1*	2,3	yes	1	3
Durvalumab	no	0	0	no	0	0	no	0	0
Dutasteride	yes	1*	3	yes	0	3	yes	1*	0
Efavirenz	yes	1	3	yes	1	2*,3	yes	1	3
Emtricitabine	no	0	0	no	0	0	no	0	0
Enalapril	yes	1*	3*	yes	1*	3*	no	0	0
Enoxaparin	no	0	0	no	0	0	no	0	0
Entacapone	yes	1	3	yes	0	3*	yes	1	3*
Enzalutamide	yes	1	3	yes	1	2,3	yes	1	3
Ephedrine	no	0	0	no	0	0	no	0	0
Epinephrine	yes	1	3*	yes	1	3*	yes	1	3*
Epirubicin	yes	0	3	yes	0	3	no	0	3
Eplerenone	yes	1*	3	yes	1*	3	yes	1*	3
Erenumab	no	0	0	no	0	0	no	0	0
Ergocalciferol	no	0	0	no	0	0	no	0	0
Erlotinib	yes	1	3	yes	1	2,3	yes	1	3
Erythromycin	yes	1	3	yes	1	3	yes	1	3
Erythropoietin	no	0	0	no	0	0	no	0	0
Escitalopram	yes	1	3	yes	1*	3	yes	1	3
Eslicarbazepine	yes	1	3*	yes	1	3*	yes	1	3*
Esomeprazol	yes	1	3	yes	1*	3	yes	1	3
Estradiol	yes	1*	3	yes	1*	2,3	yes	1*	3
Estrogens	yes	1*	3	yes	1*	2,3	yes	1*	3
Eszopiclone	yes	1*	3	yes	1*	3	yes	1*	3
Etanercept	no	0	0	no	0	0	no	0	0
Ethambutol	no	0	0	no	0	0	no	0	0
Ethanol	yes	1	3	yes	1	2*,3	yes	1	3
Etoposide	yes	1	3	yes	1	3	yes	1	3
Everolimus	yes	1	3	yes	1*	3	yes	1	3
Evolocumab	no	0	0	no	0	0	no	0	0
Ezetimibe	yes	1	3	yes	1	3	yes	1	3*
Famciclovir	no	0	0	no	0	0	no	0	0
Famotidine	yes	1*	3*	yes	1*	3*	yes	1*	3*
Febuxostat	no	0	0	no	0	0	no	0	0
Felodipine	yes	1	3	yes	1	2*,3	yes	1	3
Fenfluramine	yes	1	3*	yes	1*	3*	yes	1	3*
Fenofibrate	yes	1	3	yes	1	3	yes	1	3*
Fentanyl	yes	1*	3	yes	1*	3	yes	1*	3
Ferrous Gluconate	no	0	0	no	0	0	no	0	0

Ferrous Sulfate Anhydrous	no	0	0	no	0	0	no	0	0
Fexofenadine	yes	0	3	yes	0	3	no	0	0
Finasteride	yes	1*	3	yes	1*	3	yes	1*	3
Fingolimod	yes	1*	3*	yes	1*	3*	yes	1*	3*
Fish Oil	yes	1*	3	yes	1*	3	yes	1*	3
Fluconazole	yes	1	3*	yes	1	2*,3*	yes	1	3*
Fludarabine	no	0	0	no	0	0	no	0	0
Fludrocortisone	yes	1*	3	yes	1*	3	yes	1*	3
Flunitrazepam	yes	1*	3	yes	1*	2,3	yes	1*	3
Fluorouracil	yes	1	3	yes	1	2*,3	yes	1	3
Fluoxetine	yes	1	3	yes	1	2,3	yes	1	3
Flupentixol	yes	1*	3*	yes	1*	3*	no	0	0
Flurazepam	yes	1*	3	yes	1*	3	yes	1*	3
Fluticasone	yes	1	3	yes	1	3	yes	1	3
Fluticasone Propionate	yes	1	3	yes	1	3	yes	1	3
Folic Acid	no	0	0	no	0	0	no	0	0
Formoterol	yes	1*	3	yes	1*	2,3	yes	1*	3
Fosamprenavir	yes	1	3	yes	1	3	yes	1	3
Fosaprepitant	yes	1	3	yes	1	2*,3	yes	1	3
Fosinopril	no	0	0	no	0	0	no	0	0
Furosemide	no	0	0	no	0	0	no	0	0
Gabapentin	no	0	0	no	0	0	no	0	0
Gabapentin Enacarbil	no	0	0	no	0	0	no	0	0
Garlic	no	0	0	no	0	0	no	0	0
Gemcitabine	yes	0	3	yes	0	3	no	0	0
Gemfibrozil	yes	1	3	yes	1	2*,3	yes	1	3
Glatiramer	no	0	0	no	0	0	no	0	0
Glecaprevir	yes	1	3	yes	1	3	yes	1	3*
Glimepiride	yes	1*	3	yes	1*	2	yes	1*	0
Glipizide	yes	1*	3	yes	1*	2	yes	1*	0
Glucosamine	no	0	0	no	0	0	no	0	0
Glyburide	yes	1	3	yes	1	2,3	yes	1	3
Gold	-	-	-	-	-	-	-	-	-
Granisetron	yes	1*	3	yes	1*	2,3	yes	1*	3
Guaifenesin	no	0	0	no	0	0	no	0	0
Haloperidol	yes	1	3	yes	1	2,3	yes	1	3
Heparin	no	0	0	no	0	0	no	0	0
Hesperidin	no	0	0	no	0	0	no	0	0
Human Interferon Beta	yes	1*	3*	yes	1*	3*	yes	1*	4*
Hyaluronic Acid	no	0	0	no	0	0	no	0	0
Hydralazine	yes	1	3*	yes	1	3*	yes	1	3*

Hydrochlorothiazide	no	0	0	no	0	0	no	0	0
Hydrocodone	yes	1*	3	yes	1*	2,3	yes	1*	3
Hydrocortisone	yes	1	3	yes	1	2*,3	yes	1	3
Hydromorphone	yes	1*	3	yes	1*	2	yes	1*	0
Hydroxy-chloroquine	yes	1	3	yes	1*	3	yes	1	3
Hydroxyzine	yes	1*	3	yes	1*	3	yes	1*	3
Hyoscyamine	no	0	0	no	0	0	no	0	0
Ibandronate	no	0	0	no	0	0	no	0	0
Ibuprofen	yes	1*	3	yes	1*	2,3	yes	1*	3
Imatinib	yes	1	3	yes	1	2,3	yes	1	3
Imidazole Salicylate	-	-	-	-	-	-	-	-	-
Indapamide	yes	1*	3	yes	1*	3	yes	1*	3
Infliximab	no	0	0	no	0	0	no	0	0
Influenza Virus Vaccine	-	-	-	-	-	-	-	-	-
Insulin Aspart	yes	1*	3*	yes	1*	3*	yes	1*	3*
Insulin Detemir	yes	1*	3*	yes	1*	3*	yes	1*	3*
Insulin Glargine	yes	1*	3*	yes	1*	3*	yes	1*	3*
Insulin Human	yes	1*	3*	yes	1*	3*	yes	1*	3*
Insulin Lispro	yes	1*	3*	yes	1*	3*	yes	1*	3*
Interferon alfa-n1	yes	1*	3*	yes	1*	3*	yes	1*	3*
Interferon beta-1a	yes	1*	3*	yes	1*	3*	yes	1*	3*
Interferon beta-1b	yes	1*	3*	yes	1*	3*	yes	1*	3*
Ipilimumab	no	0	0	no	0	0	no	0	0
Ipratropium	no	0	0	no	0	0	no	0	0
Irbesartan	yes	1	3	yes	1	2,3*	yes	1	3*
Iron	no	0	0	no	0	0	no	0	0
Isosorbide Dinitrate	no	0	0	no	0	0	no	0	0
Isosorbide Mononitrate	yes	1*	3	yes	1*	3	yes	1*	3
Isotretinoin	yes	1*	3	yes	1*	3	yes	1*	3
Keratin	-	-	-	-	-	-	-	-	-
Ketoconazole	yes	1	3	yes	1	2*,3	yes	1	3
Krill Oil	-	-	-	-	-	-	-	-	-
Labetalol	yes	1	3	yes	1*	3	yes	1	3
Lacosamide	yes	1*	3	yes	1*	2,3	yes	1*	3
Lactic Acid	no	0	0	no	0	0	no	0	0
Lactobacillus Acidophilus	-	-	-	-	-	-	-	-	-
Lactulose	no	0	0	no	0	0		0	0
Lamivudine	yes	1*	3	yes	1*	3	yes	1*	0
Lamotrigine	yes	1*	3	yes	1*	3	no	0	0
Lanreotide	yes	1	3*	yes	1	3*	yes	1	3*

Lansoprazole	yes	1	3	yes	1	2*,3	yes	1	3
Lapatinib	yes	1	3	yes	1	3	yes	1	3
Latanoprost	no	0	0	no	0	0	no	0	0
Lavender Oil	-	-	-	-	-	-	-	-	-
Ledipasvir	yes	0	3	yes	0	3	no	0	0
Leflunomide	yes	1	3	yes	1	2,3	yes	1	3
Lenalidomide	yes	0	3	yes	0	3	no	0	0
Lenvatinib	yes	1	3	yes	1	2*,3	yes	1	3
Letrozole	yes	1	3	yes	1*	3	yes	1	3
Leucovorin	no	0	0	no	0	0	no	0	0
Levetiracetam	yes	0	3	yes	0	3	no	0	0
Levodopa	no	0	0	no	0	0	no	0	0
Levofloxacin	yes	1	3	yes	1	2*,3	yes	1	3
Levomefolic Acid	no	0	0	no	0	0	no	0	0
Levosalbutamol	yes	1	3*	yes	1	3*	yes	1	3*
Levothyroxine	yes	0	3*	yes	0	3*	no	0	0
Lidocaine	yes	1	3	yes	1*	2,3	yes	1	3
Linagliptin	yes	1	3	yes	1	3	yes	1	3
Linezolid	no	0	0	no	0	0	no	0	0
Liothyronine	yes	1*	3*	yes	1*	3*	no	0	0
Liotrix	yes	1*	3	yes	1*	3	yes	1*	3
Lisinopril	no	0	0	no	0	0	no	0	0
Lithium Aspartate	no	0	0	no	0	0	no	0	0
Lithium Carbonate	no	0	0	no	0	0	no	0	0
Loperamid	yes	1	3	yes	1	3	yes	1	3
Loratadine	yes	1	3	yes	1	2,3	yes	1	3
Lorazepam	yes	1*	3	yes	1*	3	yes	1*	3
Losartan	yes	1	3	yes	1	2,3	yes	1	3
Lovastatin	yes	1	3	yes	1	3	yes	1	3
Loxapine	no	0	0	no	0	0	no	0	0
Lubiprostone	no	0	0	no	0	0	no	0	0
Lurasidone	yes	1*	3	yes	1*	3	yes	1*	3
Lysergic Acid Diethylamide	yes	1*	3	yes	1*	3	yes	1*	3
Magnesium	-	-	-	-	-	-	-	-	-
Magnesium Aspartate	-	-	-	-	-	-	-	-	-
Magnesium Chloride	no	0	0	no	0	0	no	0	0
Magnesium Hydroxide	no	0	0	no	0	0	no	0	0
Magnesium Oxide	no	0	0	no	0	0	no	0	0
Meclizine	yes	1*	3	yes	0	3	yes	1*	3
Megestrol Acetate	yes	1*	3	yes	1*	3	yes	1*	3
Melatonin	yes	1*	3	yes	1*	2,3	yes	1	3

Meloxicam	yes	1*	3	yes	1*	2,3	yes	1*	3
Memantine	yes	1	3*	yes	1*	3*	yes	1	3*
Menthol	yes	1*	3	yes	1*	3	yes	1*	3
Meperidine	yes	1	3	yes	1	3	yes	1	3
Meprobamate	no	0	0	no	0	0	no	0	0
Mesalazine	no	0	0	no	0	0	no	0	0
Metamizole	yes	1	3*	yes	1	3*	yes	1	3*
Metformin	no	0	0	no	0	0	no	0	0
Methadone	yes	1	3	yes	1	2,3	yes	1	3
Meth-amphetamine	yes	1*	3	yes	0	3	yes	1*	3
Methocarbamol	no	0	0	no	0	0	no	0	0
Methotrexate	yes	1*	3	yes	1*	3	yes	1*	3
Metho-trimeprazine	yes	1	3	yes	1*	3	yes	1	3
Methsuximide	yes	1	3	yes	1*	3	yes	1	3
Methyl pyrrolidone	-	-	-	-	-	-	-	-	-
Methylcellulose	no	0	0	no	0	0	no	0	0
Methylcobalamin	no	0	0	no	0	0	no	0	0
Methylphenidate	yes	0	3	yes	0	3	no	0	0
Methyl-prednisolone	yes	1	3	yes	1	2*,3	yes	1	3
Methyl-testosterone	yes	1*	3	yes	1*	3	yes	1*	3
Metoclopramide	yes	1	3	yes	1*	3	yes	1	3
Metolazone	no	0	0	no	0	0	no	0	0
Metoprolol	yes	1	3	yes	1*	3	yes	1	3
Metronidazole	yes	1	3	yes	1	2*,3	yes	1	3
Midodrine	yes	1*	3	yes	0	3	yes	1*	3
Midomafetamine	yes	1*	3	yes	0	3	yes	1*	3
Minocycline	no	0	0	no	0	0	no	0	0
Mirtazapine	yes	1	3	yes	1	3	yes	1	3
Modafinil	yes	1	3	yes	1	2*,3	yes	1	3
Mometasone	yes	1	3	yes	1	3	yes	1	3
Mometasone Furoate	yes	1	3	yes	1	3	yes	1	3
Montelukast	yes	1*	3	yes	1*	2,3	yes	1*	3
Morphine	yes	1*	3	yes	1*	3	yes	1*	3
Moxifloxacin	yes	1*	3*	yes	1*	3*	yes	1*	3*
Mycophenolic Acid	yes	0	3	no	0	0	no	0	0
Nabumetone	yes	1*	3	yes	1*	2,3	yes	1*	3
Naldemedine	yes	0	3	yes	0	3	no	0	0
Naloxone	yes	1	3	yes	1	3	yes	1	3*
Naltrexone	no	0	0	no	0	0	no	0	0
Naphazoline	no	0	0	no	0	0	no	0	0

Naproxen	yes	1*	3	yes	1*	2,3	yes	1*	3
Nebivolol	yes	1*	3	yes	1*	3	yes	1*	3
Nevirapine	yes	1	3	yes	1	2*,3	yes	1	3
Niacin	yes	1	3*	yes	1	3*	yes	1	3*
Niacinamide	yes	1	3*	yes	1	3*	yes	1	3*
Nicardipine	yes	1	3	yes	1	2*,3	yes	1	3
Nicotine	yes	1*	3	yes	1*	2,3	yes	1*	3
Nifedipine	yes	1	3	yes	1	2*,3	yes	1	3
Nitrofurantoin	yes	0	3	yes	0	3	no	0	0
Nitroglycerin	no	0	0	no	0	0	no	0	0
Nivolumab	no	0	0	no	0	0	no	0	0
Nordazepam	-	-	-	-	-	-	-	-	-
Norepinephrine	no	0	0	no	0	0	no	0	0
Nortriptyline	yes	1	3	yes	1*	3	yes	1	3
Nystatin	no	0	0	no	0	0	no	0	0
Ocrelizumab	no	0	0	no	0	0	no	0	0
Octreotide	yes	1	3*	yes	1	3*	yes	1	3*
Olanzapine	yes	1	3	yes	1	2*,3	yes	1	3
Olopatadine	yes	1*	3	yes	1*	3	yes	1*	3
Ombitasvir	yes	0	3	yes	0	3	no	0	0
Omega-3 Fatty Acids	no	0	0	no	0	0	no	0	0
Omega-6 Fatty Acids	no	0	0	no	0	0	no	0	0
Omeprazole	yes	1	3	yes	1	2,3	yes	1	3
Ondansetron	yes	1*	3	yes	1*	2,3	yes	1*	3
Opipramol	-	-	-	-	-	-	-	-	-
Orphenadrine	yes	1	3	yes	1	3	yes	1	3
Osimertinib	yes	1	3	yes	1	3	yes	1	3
Oxaliplatin	no	0	0	no	0	0	no	0	0
Oxazepam	yes	0	3	no	0	0	no	0	0
Oxcarbazepine	yes	1	3	yes	1	3	yes	1	3*
Oxybutynin	yes	1	3	yes	1	3	yes	1	3
Oxycodone	yes	1*	3	yes	1*	3	yes	1*	3
Oxymorphone	yes	1*	3	yes	1*	3	yes	1*	3
Oxyquinoline	no	0	0	no	0	0	no	0	0
Paclitaxel	yes	1	3	yes	1	3	yes	1	3
Palbociclib	yes	1	3	yes	1	3	yes	1	3
Paliperidone	yes	1*	3	yes	1*	3	yes	1*	3
Palonosetron	yes	1*	3	yes	1*	3	yes	1*	3
Pancrelipase Amylase	no	0	0	no	0	0	no	0	0
Pancrelipase Lipase	no	0	0	no	0	0	no	0	0
Pancrelipase Protease	no	0	0	no	0	0	no	0	0

Pantoprazole	yes	1	3	yes	1*	3	yes	1	3
Pantothenic Acid	no	0	0	no	0	0	no	0	0
Paritaprevir	yes	1*	3	yes	1*	3	yes	1*	3
Paroxetine	yes	1	3	yes	1	2*,3	yes	1	3
Peginterferon alfa-2a	yes	1*	3*	yes	1*	3*	yes	1*	3*
Peginterferon alfa-2b	yes	1	3*	yes	1	3*	yes	1	3*
Pembrolizumab	no	0	0	no	0	0	no	0	0
Pemetrexed	no	0	0	no	0	0	no	0	0
Pentamidine	yes	1*	3	yes	1*	2,3	yes	1*	3
Pentazocine	yes	0	3	yes	0	3	no	0	0
Perampanel	yes	1	3	yes	1	3	yes	1	3
Perindopril	no	0	0	no	0	0	no	0	0
Phencyclidine	yes	1*	3*	yes	1*	3*	no	0	0
Pheniramine	no	0	0	no	0	0	no	0	0
Phenobarbital	yes	1	3	yes	1	2,3	yes	1	3
Phenoxymethyl-penicillin	no	0	0	no	0	0	no	0	0
Phentermine	yes	1*	3	yes	1*	3	yes	1*	3
Phenylbutazone	yes	1	3	yes	1	2,3*	yes	1	3*
Phenytoin	yes	1	3	yes	1	2,3	yes	1	3
Pibrentasvir	yes	1*	3	yes	1*	3	no	0	0
Pipamperone	no	0	0	no	0	0	no	0	0
Piracetam	no	0	0	no	0	0	no	0	0
Pirfenidone	yes	1*	3	yes	1*	3	yes	1*	3
Piritramide	-	-	-	-	-	-	-	-	-
Piroxicam	yes	1*	3	yes	1*	2	yes	1*	0
Polyethylene Glycol	yes	1*	3*	yes	1*	3*	no	0	0
Posaconazole	yes	1	3	yes	1	3	yes	1	3
Potassium	no	0	0	no	0	0	no	0	0
Potassium Chloride	no	0	0	no	0	0	no	0	0
Pramipexole	no	0	0	no	0	0	no	0	0
Prasterone	yes	1*	3	yes	1*	3	yes	1*	3
Prasugrel	yes	1*	3	yes	1*	2,3	yes	1*	3
Pravastatin	yes	0	3	yes	0	3	yes	0	0
Prazosin	yes	1*	3	yes	1*	3	no	0	0
Prednisolone	yes	1	3	yes	1	3	yes	1	3
Prednisone	yes	1	3	yes	1	2*,3	yes	1	3
Pregabalin	no	0	0	no	0	0	no	0	0
Primidone	yes	1	3	yes	1	2,3	yes	1	3
Procarbazine	no	0	0	no	0	0	no	0	0
Prochlorperazine	yes	1*	3	yes	0	3	yes	1*	3
Procyclidine	no	0	0	no	0	0	no	0	0

Progesterone	yes	1	3	yes	1	2,3	yes	1	3
Promethazine	yes	1	3	yes	1	2*,3	yes	1	3
Propafenone	yes	1	3	yes	1*	3	yes	1	3
Propiverine	yes	1*	3	yes	1*	3	yes	1*	3
Propranolol	yes	1	3	yes	1*	2*,3	yes	1	3
Propyphenazone	-	-	-	-	-	-	-	-	-
Prothipendyl	-	-	-	-	-	-	-	-	-
Prucalopride	yes	1*	3	yes	1*	3	yes	1*	3
Pseudoephedrine	no	0	0	no	0	0	no	0	0
Psyllium (Plantago Seed)	no	0	0	no	0	0	no	0	0
Pyridoxine	yes	1*	3*	yes	1*	3*	yes	1*	3*
Pyrimethamine	no	0	0	no	0	0	no	0	0
Quetiapine	yes	1*	3	yes	1*	3	yes	1*	3
Quinapril	yes	0	3	yes	0	3	no	0	0
Quinidine	yes	1	3	yes	1	2,3	yes	1	3
Quinine	yes	1	3	yes	1	2,3	yes	1	3
Rabeprazole	yes	1	3	yes	1	2*,3	yes	1	3
Raloxifene	yes	1	3	yes	1	3	yes	1	3*
Ramipril	no	0	0	no	0	0	no	0	0
Ranitidine	yes	1	3	yes	1	3	yes	1	3
Repaglinide	yes	1*	3	yes	1*	3	yes	1*	3
Ribavirin	no	0	0	no	0	0	no	0	0
Riboflavin	no	0	0	no	0	0	no	0	0
Rifampin	yes	1	3*	yes	1	2*,3*	yes	1	3*
Rimantadine	no	0	0	no	0	0	no	0	0
Riociguat	yes	1*	3	yes	1*	2,3	yes	1*	3
Risedronic Acid	no	0	0	no	0	0	no	0	0
Risperidone	yes	1	3	yes	1*	3	yes	1	3
Ritonavir	yes	1	3	yes	1	2*,3	yes	1	3
Rituximab	no	0	0	no	0	0	no	0	0
Rivaroxaban	yes	1*	3	yes	1*	3	yes	1*	3
Rivastigmine	no	0	0	no	0	0	no	0	0
Rofecoxib	yes	1	3	yes	1	2,3	yes	1	3
Ropinirole	yes	0	3	yes	0	3	yes	0	3
Rosiglitazone	yes	1	3	yes	1*	3	yes	1	3
Rosuvastatin	yes	1*	3	yes	1*	2	yes	1*	0
Rucaparib	yes	1	3	yes	1	2*,3	yes	1	3
Salbutamol	yes	1	3*	yes	1	3*	yes	1	3*
Salicylic Acid	yes	1*	3	yes	1*	2	yes	1*	0
Salmeterol	yes	1*	3	yes	1*	3	yes	1	0
Sargramostim	no	0	0	no	0	0	no	0	0
Scopolamine	yes	1*	3*	yes	1*	3*	no	0	0
Selegiline	yes	1	3	yes	1*	2,3	yes	1	3

Sennosides	no	0	0	no	0	0	no	0	0
Serine	no	0	0	no	0	0	no	0	0
Serrapeptase	-	-	-	-	-	-	-	-	-
Sertraline	yes	1	3	yes	1	2,3	yes	1	3
Sevelamer	no	0	0	no	0	0	no	0	0
Sildenafil	yes	1	3	yes	1	2,3	yes	1	3
Silodosin	yes	1*	3	yes	1*	3	yes	1*	3
Simvastatin	yes	1	3	yes	1	2*,3	yes	1	3
Sipuleucel-T	no	0	0	no	0	0	no	0	0
Sitagliptin	yes	1*	3	yes	1*	3	yes	1*	3
Sodium Aurothiomalate	no	0	0	no	0	0	no	0	0
Sodium Bicarbonate	no	0	0	no	0	0	no	0	0
Sodium Chloride	no	0	0	no	0	0	no	0	0
Sodium Citrate	no	0	0	no	0	0	no	0	0
Sodium Lauryl Sulfoacetate	no	0	0	no	0	0	no	0	0
Sodium Oxybate	no	0	0	no	0	0	no	0	0
Sofosbuvir	yes	1*	3	yes	1*	3	no	0	0
Somatotropin	no	0	0	no	0	0	no	0	0
Sorafenib	yes	1	3	yes	1	2*,3	yes	1	3
Sorbitol	no	0	0	no	0	0	no	0	0
Sotalol	yes	1*	3	yes	1*	3	yes	1*	3
Spironolactone	yes	0	3	yes	0	3*	no	0	0
Stavudine	no	0	0	no	0	0	no	0	0
Sucralfate	no	0	0	no	0	0	no	0	0
Sulbactam	no	0	0	no	0	0	no	0	0
Sulfamethoxazole	yes	1	3	yes	1	2,3	yes	1	3
Sulfasalazine	no	0	0	no	0	0	no	0	0
Sulpiride	no	0	0	no	0	0	no	0	0
Sumatriptan	yes	0	3	yes	0	3	no	0	0
Sunitinib	yes	1	3	yes	1	3	yes	1	3
Tacrolimus	yes	1*	3	yes	1*	3	yes	1*	3
Tadalafil	yes	1*	3	yes	1*	3	yes	1*	3
Tamsulosin	yes	1*	3	yes	1*	2,3	yes	1*	3
Tapentadol	yes	1	3	yes	1*	2,3	yes	1	3
Tegaserod	yes	1	3	yes	1*	3	yes	1	3
Telaprevir	yes	1	3	yes	1	3	yes	1	3
Telmisartan	yes	1	3	yes	1*	3*	yes	1	3*
Temazepam	yes	1*	3	yes	1*	2,3	yes	1*	3
Tenofovir	yes	1*	3	yes	1*	3	yes	1*	3
Tenofovir Alafenamide	yes	1*	3	yes	1*	3	no	0	0
Tenofovir Disoproxil	yes	1*	3*	yes	1*	3*	no	0	0

Terazosin	yes	1*	3*	yes	1*	3*	no	0	0
Terbinafine	yes	1	3	yes	1	2,3	yes	1	3
Teriflunomide	yes	1*	3*	yes	1*	3*	yes	1*	3*
Teriparatide	no	0	0	no	0	0	no	0	0
Testosterone	yes	1	3	yes	1	2,3	yes	1	3
Testosterone Undecanoate	yes	1	3	yes	1	2,3	yes	1	3
Theophylline	yes	1*	3	yes	1*	2,3	yes	1	3
Thiamine	no	0	0	no	0	0	no	0	0
Timolol	yes	1*	3	yes	1*	3	yes	1*	3
Tiotropium	yes	1*	3	yes	1*	3	yes	1*	3
Tizanidine	yes	0	3	yes	0	3	yes	0	3
Tobacco Leaf	no	0	0	no	0	0	no	0	0
Tocilizumab	yes	1	3*	yes	1	3*	yes	1	3*
Tofacitinib	yes	1*	3	yes	1*	3	yes	1*	3
Tolterodine	yes	1*	3	yes	1*	2,3	yes	1*	3
Topiramate	yes	1	3	yes	1	3	yes	1	3*
Topotecan	yes	1	3	yes	1	3	yes	1	3*
Torasemide	yes	1	3	yes	1	2	yes	1	0
Tramadol	yes	1*	3	yes	1*	3	yes	1*	3
Trazodone	yes	1	3	yes	1*	3	yes	1	3
Triamcinolone	yes	1	3	yes	1	3	yes	1	3
Triamterene	yes	0	3	yes	0	3	yes	0	3
Triazolam	yes	1*	3	yes	1*	3	yes	1*	3
Trimebutine	yes	1*	3	yes	1*	3	yes	1*	3
Trimethoprim	yes	1*	3	yes	1*	2,3	yes	1*	3
Trospium	yes	1	3*	yes	1*	3*	yes	1	3*
Turmeric	-	-	-	-	-	-	-	-	-
Ubidecarenone	yes	0	3	yes	0	3	no	0	0
Urelumab	-	-	-	-	-	-	-	-	-
Ustekinumab	no	0	0	no	0	0	no	0	0
Valproic Acid	yes	1	3	yes	1	2,3	yes	1	3
Valsartan	yes	1*	3	yes	1*	2	yes	1*	0
Vancomycin	no	0	0	no	0	0	no	0	0
Varenicline	no	0	0	no	0	0	no	0	0
Vedolizumab	no	0	0	no	0	0	no	0	0
Velpatasvir	yes	1*	3	yes	1*	3	yes	1*	3
Vemurafenib	yes	1	3	yes	1	2*,3	yes	1	3
Venetoclax	yes	1	3	yes	1	3	yes	1	3
Venlafaxine	yes	1	3	yes	1*	3	yes	1	3
Verapamil	yes	1	3	yes	1	2,3	yes	1	3
Vilanterol	yes	1*	3	yes	1*	3	yes	1*	3
Vincristine	yes	1*	3	yes	1*	3	yes	1*	3
Vindesine	yes	1*	3	yes	1*	3	yes	1*	3

Vismodegib	yes	1	3	yes	1	2,3	yes	1	3
Vitamin B12	-	-	-	-	-	-	-	-	-
Vitamin D	yes	1*	3	yes	1*	3	yes	1*	3
Vitamin E	yes	1	3	yes	1	3	yes	1	3
Warfarin	yes	1	3	yes	1	2,3	yes	1	3
Zidovudine	yes	1*	3	yes	1*	2,3	yes	1*	3
Ziprasidone	yes	1*	3	yes	1*	3	yes	1*	3
Zolpidem	yes	1*	3	yes	1*	2,3	yes	1*	3
Zonisamide	yes	1	3	yes	1*	3	yes	1	3
Zopiclone	yes	1*	3	yes	1*	2,3	yes	1*	3
Zuclopenthixol	yes	1*	3	yes	1*	3	yes	1*	3

Table 34. 'Frequency of Pharmacodynamic Reactions'. Frequency of how often side effects in each side effect category occurs. *0 = frequency ≤ 1%; 1 = frequency 1-10% (common); 2 = frequency ≥10% (very common); 1° = no frequency found, but mentioned as side effect; - = no information available*

Pharmacodynamic Reactions	Cardiovascular Side Effects	Neuropsychiatric Diseases	Effect on Infections	Sedation
Cannabidiol	0	1	2	2
Dronabinol	1	2	1	0
Nabiximols	1	1	0	1
Abatacept	1	1	2	0
Acetaminophen	1	1	0	0
Acetylcysteine	0	0	0	0
Acyclovir	0	1	0	0
Adalimumab	1	1	2	0
Alendronic Acid	0	0	0	0
Alfuzosin	1°	1	0	0
Alimemazine	1°	1°	0	1°
Alizapride	1°	1°	0	1°
Allopurinol	0	0	0	1°
Alprazolam	1	2	0	2
Amantadine	2	2	0	0
Aminosalicylic Acid	1°	1°	0	0
Amiodarone	1	1	1	0
Amisulpride	1	2	0	0
Amitriptyline	2	2	0	1
Amlodipine	1	1	0	0
Amoxapine	1	2	0	1°
Amoxicillin	0	0	1	0
Amphetamine	2	2	2	0
Ampicillin	0	0	1	0
Anakinra	0	0	2	0
Apixaban	0	0	0	0
Apremilast	0	1	2	0
Aprepitant	1	1	1	0
Aripiprazole	1	1	1	1
Armodafinil	1	1	0	0
Arnica Montana Flower	-	-	-	-
Ascorbic Acid	0	0	0	0
Aspirin	1°	1°	1	0
Atenolol	2	2	0	1
Atorvastatin	1	1	1	0
Atropine	1°	1°	0	0
Avelumab	1	2	2	1°
Azithromycin	1	1	0	0
Baclofen	2	1	1	1
Beclomethasone Dipropionate	1°	1°	2	0
Benazepril	1	0	0	1°

Benperidol	1	2	0	0
Benzatropine	1°	1°	0	0
Benzodiazepine	-	-	-	-
Benzoylecgonine	-	-	-	-
Bevacizumab	2	2	1	1
Bictegravir	0	1	0	0
Biotin	0	0	0	0
Bisacodyl	0	0	0	0
Bisoprolol	1	1	1	1
Bleomycin	1°	0	0	0
Boceprevir	1°	2	1°	2
Bosentan	1	0	2	0
Brimonidine	1	1	1	1
Brinzolamide	0	1°	1	0
Brivanib Alaninate	1°	-	-	-
Brivaracetam	0	2	0	2
Bromazepam	1°	1	0	1
Budesonide	1	1	2	0
Bumetanide	0	0	0	0
Bupivacaine	1°	1°	1°	0
Buprenorphine	1	1	1	1
Bupropion	1	2	1	2
Buspirone	1°	1	0	0
Butalbital	1°	1°	0	1°
Caffeine	1°	0	1	0
Calcium	0	0	0	0
Calcium Carbonate	0	0	0	0
Calcium Chloride	1°	0	0	0
Calcium Phosphate	0	0	0	0
Canakinumab	0	0	2	0
Candesartan	2	1	1	0
Carbamazepine	1	2	0	1
Carbazochrome	-	-	-	-
Carbidopa	1°	1°	1°	0
Carboplatin	0	0	1	1
Carboxymethylcellulose	0	0	0	0
Cariprazine	1	2	0	0
Carisoprodol	1°	2		1°
Carvedilol	2	1	1	1
Cefaclor	0	0	1	0
Cefepime	0	0	0	0
Ceftriaxone	0	0	0	0
Cefuroxime	0	0	1	0
Celecoxib	1	1	1	0
Cephalexin	0	1°	1°	0
Cetirizin	1	2	1	1

Cetuximab	1	2	2	2
Chlordiazepoxide	1°	1°	0	1
Chlorpromazine	1°	2	0	1°
Chlorthalidone	1	1°	0	0
Cholecalciferol	0	0	0	0
Cholestyramine	0	1°	0	0
Chondroitin Sulfate	0	0	0	0
Cilostazol	1	1	1	0
Ciprofloxacin	1°	1	1	0
Cisplatin	1°	0	1°	0
Citalopram	1	1	1	1
Citicoline	1°	-	-	-
Citric Acid	0	0	0	0
Clavulanic Acid	0	0	1	0
Clindamycin	1°	0	1	0
Clobetasol	0	0	1	0
Clobetasol Propionate	0	0	1	0
Clonazepam	1°	2	1	1
Clonidine	2	2	0	2
Clopidogrel	1	1°	0	0
Clotrimazole	0	0	0	0
Clozapine	2	2	0	2
Cobalamin	1°	0	1	0
Cobimetinib	2	0	0	0
Cocaine	2	1°	0	0
Codeine	1°	2	0	1°
Colchicine	0	0	0	0
Colestipol	1°	1°	0	0
Collagen	0	0	0	0
Conjugated Estrogens	0	1	1	0
Corticotropin	2	2	2	0
Cortisone Acetate	1°	1	1°	1°
Crizotinib	2	2	2	0
Curcumin	0	0	0	0
Cyclizine	1°	0	0	0
Cyclobenzaprine	1°	1°	0	1
Cyclophosphamide	1°	1°	0	0
Cyclosporine	2	2	2	0
Dabigatran Etexilate	1°	0	0	0
Daclatasvir	0	0	0	0
Dalfampridine	0	1	2	1
Dantrolene	1	1	0	1°
Danvatirsen	-	-	-	-
Daprodustat	-	-	c	-
Darbepoetin Alfa	2	0	0	0
Darunavir	0	0	0	0

Dasabuvir	0	1	0	0
Dasatinib	2	1	2	0
Deflazacort	1	1	2	0
Denosumab	2	1	1	0
Desloratadine	0	1	2	1°
Desmopressin	1	1	1	0
Desvenlafaxine	1	2	0	0
Dexamethasone	1°	1°	1°	0
Dextroamphetamine	1°	1°	0	0
Dextromethorphan	0	1°	0	1°
Dextropropoxyphene	0	0	0	0
Diamorphine	-	1°	-	-
Diazepam	1	2	1	1
Diclofenac	1	1°	1	0
Dicyclomine	1°	2	0	1°
Digoxin	1	1	0	0
Dihydrocodeine	0	2	0	2
Diltiazem	1	1	1	0
Dimenhydrinate	1°	1	0	2
Diosmin	1°	-	-	-
Diphenhydramine	1°	1°	0	1
Diphenoxylate	1°	1°	0	1°
Docusate	0	0	0	0
Dofetilide	2	1	1	0
Domperidone	0	1°	0	1°
Donepezil	1	1	1	0
Dopamine	1°	1°	0	0
Dorzolamide	0	1°	0	0
Doxazosin	1	2	1	0
Doxepin	1°	1°	1°	1°
Doxorubicin	2	0	1	0
Doxycycline	1	1	1	0
Droperidol	1°	1°	0	0
Duloxetine	1	2	1	1°
Durvalumab	2	1	2	0
Dutasteride	1°	1°	0	0
Efavirenz	0	2	0	0
Emtricitabine	0	2	2	0
Enalapril	1	1	0	0
Enoxaparin	1	1	0	0
Entacapone	1°	1	0	1°
Enzalutamide	2	2	2	0
Ephedrine	1°	1°	0	0
Epinephrine	1°	1°	0	0
Epirubicin	1	1°	2	0
Eplerenone	1°	1	0	0

Erenumab	1°	0	0	0
Ergocalciferol	0	0	0	0
Erlotinib	1	1	2	0
Erythromycin	1°	1°	0	0
Erythropoietin	1°	0	0	0
Escitalopram	1	1	1	1
Eslicarbazepine	1	2	1	0
Esomeprazol	0	1	1	0
Estradiol	1°	1°	1	0
Estrogens	1	1	1	0
Eszopiclone	1	1	1	0
Etanercept	0	0	2	0
Ethambutol	1°	1°	1°	0
Ethanol	1°	1°	0	1°
Etoposide	1	1	1°	0
Everolimus	2	2	2	0
Evolocumab	1°	1°	1	0
Ezetimibe	0	0	1	0
Famciclovir	1°	1	0	0
Famotidine	1°	1	1°	1°
Febuxostat	1	0	0	0
Felodipine	1	1	1	0
Fenfluramine	1°	1°	0	1°
Fenofibrate	1	1°	1	0
Fentanyl	1	2	1	2
Ferrous Gluconate	0	0	0	0
Ferrous Sulfate Anhydrous	0	0	0	0
Fexofenadine	0	1	1	1
Finasteride	1	0	0	0
Fingolimod	1	1	2	0
Fish Oil	1	0	0	0
Fluconazole	1°	1	0	1°
Fludarabine	1	2	2	0
Fludrocortisone	1°	1°	1°	0
Flunitrazepam	0	1°	0	1°
Fluorouracil	1°	1°	1	0
Fluoxetine	1	1	1°	2
Flupentixol	1°	1°	0	1°
Flurazepam	1°	1°	0	1°
Fluticasone	1	1	1	0
Fluticasone Propionate	1	1	1	0
Folic Acid	0	1°	0	0
Formoterol	1	1	1	0
Fosamprenavir	0	0	0	0
Fosaprepitant	1°	1	1	0
Fosinopril	1	1	1	0

Furosemide	1°	1°	0	0
Gabapentin	1	2	1	2
Gabapentin Enacarbil	1	1	0	2
Garlic	1°	0	0	0
Gemcitabine	2	1	2	1
Gemfibrozil	1	1	1°	0
Glatiramer	1	2	2	0
Glecaprevir	1°	0	0	1
Glimepiride	0	1	0	1
Glipizide	0	1	0	1
Glucosamine	0	0	0	0
Glyburide	0	0	0	0
Gold	-	-	-	-
Granisetron	1	1	0	1
Guaifenesin	1°	0	0	1°
Haloperidol	1°	2	1°	2
Heparin	0	0	0	0
Hesperidin	0	0	0	0
Human Interferon Beta	-	-	-	-
Hyaluronic Acid	1	1	1	0
Hydralazine	1	1°	0	0
Hydrochlorothiazide	1°	1°	0	0
Hydrocodone	1	1	1	1
Hydrocortisone	1°	1°	1°	0
Hydromorphone	1	2	0	1°
Hydroxychloroquine	1°	1°	0	0
Hydroxyzine	1°	1°	0	1°
Hyoscyamine	1°	1°	0	1°
Ibandronate	1	1	2	0
Ibuprofen	1	1	1°	0
Imatinib	1	1	2	2
Imidazole Salicylate	1°	1°	1°	1°
Indapamide	1	1	1	1
Infliximab	1	0	2	0
Influenza Virus Vaccine	1°	1°	1°	2
Insulin Aspart	1°	0	2	0
Insulin Detemir	1°	0	2	0
Insulin Glargine	2	1	2	0
Insulin Human	1°	0	0	0
Insulin Lispro	1°	0	1	0
Interferon alfa-n1	1°	1°	1°	0
Interferon beta-1a	1	2	1	1
Interferon beta-1b	1	2	1°	1°
Ipilimumab	0	2	1	1°
Ipratropium	0	1	1	0
Irbesartan	1	1	1	0

Iron	-	1°	-	1°
Isosorbide Dinitrate	1	1	0	0
Isosorbide Mononitrate	1	1	1	0
Isotretinoin	1°	1°	1°	1°
Keratin	-	-	-	-
Ketoconazole	1°	1°	0	0
Krill Oil	1	0	0	0
Labetalol	1	1	0	1
Lacosamide	1°	1	0	1
Lactic Acid	-	-	-	-
Lactobacillus Acidophilus	0	0	1°	0
Lactulose	0	0	0	0
Lamivudine	0	2	2	0
Lamotrigine	0	0	1°	0
Lanreotide	2	1	0	0
Lansoprazole	0	1	1°	0
Lapatinib	1	2	0	0
Latanoprost	1°	0	1	0
Lavender Oil	-	-	-	-
Ledipasvir	0	1	0	0
Leflunomide	1	1	1°	0
Lenalidomide	1	2	2	1
Lenvatinib	2	2	1	0
Letrozole	1	1	1	1
Leucovorin	0	0	1	1
Levetiracetam	1	2	2	2
Levodopa	2	2	1	1°
Levofloxacin	0	1	0	0
Levomefolic Acid	-	1°	-	-
Levosalbutamol	1	1	1	0
Levothyroxine	1°	1°	0	0
Lidocaine	1°	1°	0	1°
Linagliptin	1°	0	0	0
Linezolid	1°	1	1°	0
Liothyronine	1	1°	0	0
Liotrix	1°	1°	0	0
Lisinopril	1	1	0	0
Lithium Aspartate	1°	2	0	1°
Lithium Carbonate	1°	1°	0	1°
Loperamid	1°	1	0	0
Loratadine	1°	1°	1	1
Lorazepam	1	2	0	2
Losartan	1	1	1	1
Lovastatin	1°	1°	1	1
Loxapine	1	1°	0	2
Lubiprostone	1	1	0	0

Lurasidone	1	2	2	1
Lysergic Acid Diethylamide	1°	1°	-	-
Magnesium	1°	-	-	-
Magnesium Aspartate	-	-	-	-
Magnesium Chloride	0	0	0	0
Magnesium Hydroxide	0	0	0	0
Magnesium Oxide	0	0	0	0
Meclizine	1°	1°	0	2
Megestrol Acetate	1	1	1	1°
Melatonin	1	1	0	1°
Meloxicam	1	1	1	1
Memantine	1	1	1	1
Menthol	0	0	0	0
Meperidine	1°	1°	0	1°
Meprobamate	1°	1	0	1
Mesalazine	0	1	1	0
Metamizole	0	0	0	0
Metformin	1	1	2	0
Methadone	1°	1°	0	1°
Methamphetamine	1°	1°	0	0
Methocarbamol	1°	1	0	1
Methotrexate	1°	1	1°	1°
Methotrimeprazine	1°	1°	0	1°
Methsuximide	0	1	0	1
Methyl pyrrolidone	-	-	-	-
Methylcellulose	0	0	0	0
Methylcobalamin	0	0	0	0
Methylphenidate	1	1	1	1
Methylprednisolone	1°	1°	1°	0
Methyltestosterone	1°	1°	0	0
Metoclopramide	1°	1°	0	2
Metolazone	1°	1°	0	1°
Metoprolol	1	1	0	1
Metronidazole	1°	1	1	1°
Midodrine	1	1	0	0
Midomafetamine	1°	1°	0	1°
Minocycline	1°	1	1	1
Mirtazapine	1	1	1	2
Modafinil	1	1	1	1
Mometasone	0	1	1	0
Mometasone Furoate	0	1	1	0
Montelukast	1°	1	1	1°
Morphine	1	1	0	1
Moxifloxacin	0	1	1	0
Mycophenolic Acid	2	2	2	1
Nabumetone	1	1	0	0

Naldemedine	0	1°	0	0
Naloxone	1°	1°	0	0
Naltrexone	1	1	1°	1
Naphazoline	1°	1°	0	1°
Naproxen	1	1	1	1
Nebivolol	1°	1	0	0
Nevirapine	1°	0	0	1°
Niacin	1°	1°	0	0
Niacinamide	0	0	0	0
Nicardipine	1	1	0	1
Nicotine	1°	1	0	0
Nifedipine	1	1	1	1
Nitrofurantoin	1°	1°	1°	1°
Nitroglycerin	1	1	0	0
Nivolumab	1	2	2	2
Nordazepam	-	-	-	1°
Norepinephrine	1°	1°	0	0
Nortriptyline	1	1°	0	1°
Nystatin	1°	0	0	0
Ocrelizumab	1	1	2	0
Octreotide	2	2	1	0
Olanzapine	1	2	1	2
Olopatadine	0	1	1	1
Ombitasvir	1	2	0	1
Omega-3 Fatty Acids	1	0	0	0
Omega-6 Fatty Acids	-	-	-	-
Omeprazole	0	1	1	1°
Ondansetron	1°	1	0	1
Opipramol	1	0	0	0
Orphenadrine	1°	1°	0	1°
Osimertinib	1	0	1	1
Oxaliplatin	1	1	1	1
Oxazepam	1°	1°	0	1°
Oxcarbazepine	1	2	1	2
Oxybutynin	1	2	1	2
Oxycodone	1	2	1	1
Oxymorphone	1	2	0	2
Oxyquinoline	0	0	0	0
Paclitaxel	2	0	2	0
Palbociclib	0	0	2	0
Paliperidone	1	1	1	1
Palonosetron	1	1	0	0
Pancrelipase Amylase (Pancrelipase)	1	1	1	0
Pancrelipase Lipase (Pancrelipase)	1	1	1	0

Pancrelipase Protease (Pancrelipase)	1	1	1	0
Pantoprazole	0	1	1	1°
Pantothenic Acid	1°	0	0	0
Paritaprevir	1	2	0	2
Paroxetine	1	2	1	1
Peginterferon alfa-2a	1°	2	2	2
Peginterferon alfa-2b	1°	2	1	2
Pembrolizumab	1	2	2	1°
Pemetrexed	1	2	1	0
Pentamidine	1	2	1	0
Pentazocine	1°	1	0	1°
Perampanel	1°	2	1	1°
Perindopril	1	1	1	1°
Phencyclidine	1°	1°	-	-
Pheniramine	1°	1°	-	-
Phenobarbital	1°	1°	0	1°
Phenoxymethylpenicillin	0	0	0	0
Phentermine	1°	1	0	0
Phenylbutazone	-	1°	-	-
Phenytoin	1°	1	0	1
Pibrentasvir	1°	1	0	1
Pipamperone	-	1°	-	-
Piracetam	-	1°	-	-
Pirfenidone	0	2	2	1
Piritramide	-	-	-	-
Piroxicam	1	1	1°	0
Polyethylene Glycol	0	0	0	0
Posaconazole	2	2	1	1
Potassium	1°	1°	1°	0
Potassium Chloride	1°	1°	1°	0
Pramipexole	1	1	1	1°
Prasterone	0	0	0	0
Prasugrel	1	1	0	0
Pravastatin	0	1	1	1°
Prazosin	1	1	0	1°
Prednisolone	1°	1°	1°	1°
Prednisone	1°	1°	1°	1°
Pregabalin	1	2	2	1
Primidone	0	1°	0	1°
Procarbazine	1°	1°	1°	1°
Prochlorperazine	1°	1°	1°	1°
Procyclidine	0	1°	0	0
Progesterone	1	2	1	0
Promethazine	1°	1°	0	1°
Propafenone	1	1	1	0

Propiverine	1°	1°	0	0
Propranolol	1°	1°	1°	1°
Propyphenazone	1°	-	-	-
Prothipendyl	-	-	-	-
Prucalopride	0	1	0	0
Pseudoephedrine	1°	1	0	0
Psyllium (Plantago Seed)	0	0	0	0
Pyridoxine	1°	1°	0	0
Pyrimethamine	1°	0	1°	0
Quetiapine	2	2	1	1
Quetiapine Fumarate	2	2	1	1
Quinapril	1	1	0	0
Quinidine	1°	1	1°	1
Quinine	1°	2	1°	0
Rabeprazole	1	1	1	0
Raloxifene	1	1	2	0
Ramipril	1	1	0	1
Ranitidine	1°	1	1	1
Repaglinide	1	0	1	0
Ribavirin	0	2	2	1
Riboflavin	0	0	0	0
Rifampin	1°	1°	1°	0
Rimantadine	1°	1	0	1
Riociguat	1°	2	0	0
Risedronic Acid	1	1	2	0
Risperidone	1	2	1	2
Ritonavir	1	2	0	2
Rituximab	2	2	2	0
Rivaroxaban	1°	1	1°	0
Rivastigmine	1	2	1	1
Rofecoxib	1	1	1	1
Ropinirole	2	2	1	1
Rosiglitazone	1	0	1	0
Rosuvastatin	0	1	0	1°
Rucaparib	0	2	2	2
Salbutamol	1	2	2	0
Salicylic Acid	0	1°	0	0
Salmeterol	1	1	1	0
Sargramostim	2	2	2	0
Scopolamine	0	1	1	1°
Selegiline	1	2	1	1
Sennosides	0	0	0	0
Serine	-	-	1°	-
Serrapeptase	-	-	-	-
Sertraline	1	2	1°	1°
Sevelamer	0	0	1	0

Sildenafil	1	1	1	0
Silodosin	1	1	1	0
Simvastatin	1	0	1	1°
Sipuleucel-T	1	2	1	0
Sitagliptin	1°	0	1	0
Sodium Aurothiomalate	0	1°	1°	0
Sodium Bicarbonate	0	1°	0	0
Sodium Chloride	1°	0	1°	0
Sodium Citrate	1°	1°	0	0
Sodium Lauryl Sulfoacetate	-	-	-	-
Sodium Oxybate	0	2	0	1
Sofosbuvir	0	1	0	1
Somatotropin	1°	1°	0	1°
Sorafenib	2	2	1	0
Sorbitol	1°	0	0	0
Sotalol	1	2	1	2
Spironolactone	1°	1°	0	1°
Stavudine	0	2	0	0
Sucralfate	1°	0	0	0
Sulbactam	1	1°	1°	0
Sulfamethoxazole	0	1°	1°	1°
Sulfasalazine	1°	1	1°	0
Sulpiride	1°	1	0	0
Sumatriptan	1	2	0	1
Sunitinib	2	2	2	0
Tacrolimus	2	2	2	0
Tadalafil	1	1	2	0
Tamsulosin	1	1	2	1
Tapentadol	0	2	1	1
Tegaserod	1°	1	0	1
Telaprevir	0	2	0	0
Telmisartan	1°	1	1	1°
Temazepam	0	1	0	1
Tenofovir	0	1	1	0
Tenofovir Alafenamide	0	1	0	0
Tenofovir Disoproxil	0	2	1	1
Terazosin	1	1	1	1
Terbinafine	0	0	1	0
Teriflunomide	1	2	1	0
Teriparatide	1	1	1	0
Testosterone	1	1	1	0
Testosterone Undecanoate	1	1	1	0
Theophylline	1°	1°	0	0
Thiamine	0	0	0	0
Timolol	1	1	0	0
Tiotropium	1	1	2	0

Tizanidine	2	2	1	1°
Tobacco Leaf	-	-	-	-
Tocilizumab	1	1	1	0
Tofacitinib	1	1°	2	0
Tolterodine	0	1	1	0
Topiramate	1	2	2	1°
Topotecan	0	1	2	1
Torasemide	1	0	1	0
Tramadol	1	2	1	1
Trazodone	1	2	0	2
Triamcinolone	1°	1°	1°	0
Triamterene	0	1°	1°	0
Triazolam	1°	2	0	1°
Trimebutine	0	1	0	0
Trimethoprim	0	0	1°	0
Trospium	1	1	1	0
Turmeric	-	-	-	-
Ubidecarenone	-	-	-	-
Urelumab	-	-	-	-
Ustekinumab	0	1	2	0
Valproic Acid	1	2	2	1°
Valsartan	1	1	1	0
Vancomycin	2	0	1	0
Varenicline	1	2	1	1
Vedolizumab	0	1	1	0
Velpatasvir	0	2	0	1
Vemurafenib	2	2	2	1
Venetoclax	2	2	2	0
Venlafaxine	1	2	1	1
Verapamil	1	1	0	1
Vilanterol	1	1°	1	0
Vincristine	1°	1°	0	0
Vindesine	0	1°	0	0
Vismodegib	0	2	0	0
Vitamin B12	1°	1	2	0
Vitamin D	0	0	0	0
Vitamin E	0	0	1°	0
Warfarin	1°	0	0	0
Zidovudine	1	1	0	1
Ziprasidone	2	1	1	0
Zolpidem	1	1	1	1
Zonisamide	2	0	1	1°
Zopiclone	1°	1°	0	1°
Zuclopenthixol	2	1	0	0

Table 35. List with Interesting Drugs that might Interact with CBD. *Column 1: Drugs; Column 2: Number of reports from people over or equal 50 years old that contain this drug; Column 3: Number of reports from people under 50 years old that contain this drug; Column 4: Number of reports from people with no defined age that contain this drug; Column 5: Prediction of correlation in between pharmacokinetic and pharmacodynamic interaction from 'PK-PD-Correlation' Table; Column 6: Known interactions from literature (no guarantee of completeness); Column 7: Interaction regarding 'Wechselwirkungscheck' on DocCheck and 'drug interactions checker' on drug.com (see 2.2.2.3 drug interactions); Column 8: Note, if drug might be interesting for further analysis or future studies; Colors: light red - over 1% frequency, dark red - over 10% frequency; Additional information e.g data sources, details about interaction etc. is available in Excel file 'List with Interesting Drugs'*

Drugs	# of reports ≥ 50 years	# of reports < 50 years	# of reports not defined age	Drug Interaction Prediction (# of correlation)	Known Interactions (Literature)	Interactions Checker	INTERESTING DRUGS
Abatacept	0	0	41	0		no	no
Acetaminophen	0	1	14	0	yes	yes	
Acetylcysteine	0	0	1	0		no	
Acyclovir	0	0	3	0		no	
Adalimumab	0	0	0	0		no	
Alendronic Acid	0	0	0	0		no	
Alfuzosin	0	0	0	0		yes	
Alimemazine	0	0	1	0		-	
Alizapride	0	0	0	0		no	
Allopurinol	0	0	1	0		no	
Alprazolam	0	0	8	2		yes	
Amantadine	0	0	2	0		no	
Aminosalicylic Acid	0	0	0	0		yes	
Amiodarone	0	0	0	1		yes	
Amisulpride	0	0	0	0		no	
Amitriptyline	0	0	7	2		yes	
Amlodipine	0	0	5	0		yes	
Amoxapine	0	0	0	1		yes	
Amoxicillin	0	0	15	0		no	
Amphetamine	0	0	0	2		no	
Ampicillin	0	0	0	0		no	
Anakinra	0	0	1	0		no	
Apixaban	0	0	0	0		no	
Apremilast	0	0	0	1		no	
Aprepitant	0	0	0	1		yes	
Aripiprazole	0	0	27	2		yes	
Armodafinil	0	0	0	0		no	
Arnica Montana Flower	0	0	0	0		no	
Ascorbic Acid	0	3	168	0		no	yes
Aspirin	0	0	18	1		no	
Atenolol	0	0	3	2		yes	
Atorvastatin	0	0	14	1		yes	
Atropine	0	0	6	0		no	
Avelumab	0	0	0	0		no	
Azithromycin	0	0	10	0		yes	
Baclofen	0	2	59	0		yes	no
Beclomethasone Dipropionate	0	0	0	1		no	

Benazepril	0	0	1	0		yes	
Benperidol	0	0	0	0		-	
Benzatropine	0	0	0	0		-	
Benzodiazepine	0	1	0	0		-	
Benzoylecgonine	0	0	0	0		-	
Bevacizumab	0	0	0	0		no	
Bictegravir	0	0	0	0		no	
Biotin	0	0	7	0		no	
Bisacodyl	0	0	14	0		no	
Bisoprolol	0	0	0	0		no	
Bleomycin	0	0	0	0		no	
Boceprevir	0	0	0	2		yes	
Bosentan	0	0	0	1		yes	
Brimonidine	0	0	0	0		yes	
Brinzolamide	0	0	0	1		no	
Brivanib Alaninate	0	0	0	0		-	
Brivaracetam	0	1	6	2		yes	
Bromazepam	0	0	0	1		-	
Budesonide	0	1	28	1		no	
Bumetanide	0	0	0	0		no	
Bupivacaine	0	0	0	0		no	
Buprenorphine	0	0	0	2		yes	
Bupropion	0	0	0	3		yes	
Buspirone	0	0	6	0		yes	
Butalbital	0	0	0	0		yes	
Caffeine	0	0	0	1		no	
Calcium	0	2	57	0		no	yes
Calcium Carbonate	0	2	16	0		no	
Calcium Chloride	0	0	0	0		no	
Calcium Phosphate	0	0	2	0		no	
Canakinumab	0	0	0	0		no	
Candesartan	0	0	0	1		no	
Carbamazepine	0	0	31	2	no	yes	no
Carbazochrome	0	0	0	0		-	
Carbidopa	0	0	7	0		no	
Carboplatin	0	0	0	0		no	
Carboxymethylcellulose	0	0	0	0		no	
Cariprazine	0	0	0	1		yes	
Carisoprodol	0	0	0	1		yes	
Carvedilol	0	1	1	2		no	
Cefaclor	0	0	0	1		no	
Cefepime	0	0	0	0		no	
Ceftriaxone	0	0	0	0		no	
Cefuroxime	0	0	1	0		no	
Celecoxib	0	0	10	1		yes	
Cephalexin	0	0	11	0		no	
Cetirizine	0	1	84	3		yes	no

Cetuximab	0	0	0	0		no	
Chlordiazepoxide	0	0	0	1		yes	
Chlorpromazine	0	0	0	1		yes	
Chlorthalidone	0	0	0	0		no	
Cholecalciferol	0	0	0	0		no	
Cholestyramine	0	0	1	0		no	
Chondroitin Sulfate	0	0	0	0		no	
Cilostazol	0	0	0	1		no	
Ciprofloxacin	0	1	5	1		yes	
Cisplatin	0	0	0	0		no	
Citalopram	0	0	15	2		yes	
Citicoline	0	0	0	0		no	
Citric Acid	0	0	1	0		no	
Clavulanic Acid	0	0	1	0		yes	
Clindamycin	0	0	7	1		no	
Clobetasol	0	0	0	1		no	
Clobetasol Propionate	0	0	0	1		no	
Clonazepam	0	16	285	3	no	yes	no
Clonidine	0	0	70	2		yes	yes
Clopidogrel	0	0	1	0		no	
Clotrimazole	0	0	3	0		yes	
Clozapine	0	0	4	2		yes	
Cobalamin	0	0	0	0		no	
Cobimetinib	0	0	0	0		yes	
Cocaine	0	0	0	0		no	
Codeine	0	0	0	1		yes	
Colchicine	0	0	0	0		no	
Colestipol	0	0	0	0		no	
Collagen	0	0	0	0		no	
Conjugated Estrogens	0	0	0	1		no	
Corticotropin	0	0	0	2		no	
Cortisone Acetate	0	0	0	0		no	
Crizotinib	0	0	0	2		yes	
Curcumin	0	0	1	0		-	
Cyclizine	0	0	0	0		yes	
Cyclobenzaprine	0	0	1	1		yes	
Cyclophosphamide	0	0	0	0		no	
Cyclosporine	0	0	2	2		yes	
Dabigatran Etexilate	0	0	0	0		no	
Daclatasvir	0	0	0	0		no	
Dalfampridine	0	0	0	0		no	
Dantrolene	0	0	0	0		yes	
Danvatirsen	0	0	0	0		-	
Daprodustat	0	0	0	0		-	
Darbepoetin Alfa	0	0	0	0		no	
Darunavir	0	0	0	0		yes	
Dasabuvir	0	0	0	0		no	

Dasatinib	0	0	0	1		no	
Deflazacort	0	0	0	1		no	
Denosumab	0	0	2	0		no	
Desloratadine	0	0	2	0		no	
Desmopressin	0	0	7	0		no	
Desvenlafaxine	0	0	0	1		yes	
Dexamethasone	0	0	1	0		no	
Dextroamphetamine	0	0	15	0		no	
Dextromethorphan	0	0	2	0	yes	yes	
Dextropropoxyphene	0	0	0	0		-	
Diamorphine	0	0	0	0		-	
Diazepam	0	3	143	3		yes	no
Diclofenac	0	0	3	1	yes	yes	
Dicyclomine	0	0	1	0		no	
Digoxin	0	0	0	0		no	
Dihydrocodeine	0	0	1	2		yes	
Diltiazem	0	0	0	1	yes	yes	
Dimenhydrinate	0	0	0	0		yes	
Diosmin	0	0	0	0		-	
Diphenhydramine	0	0	9	1		yes	
Diphenoxylate	0	0	1	0		yes	
Docusate	0	2	28	0		no	
Dofetilide	0	0	0	1		no	
Domperidone	0	0	0	0		-	
Donepezil	0	0	1	1		no	
Dopamine	0	0	0	0		no	
Dorzolamide	0	0	1	0		no	
Doxazosin	0	0	4	2		no	
Doxepin	0	0	4	0		yes	
Doxorubicin	0	0	0	1	yes	no	
Doxycycline	0	0	7	1		no	
Droperidol	0	0	0	0		yes	
Duloxetine	0	0	4	2		yes	
Durvalumab	0	0	0	0		no	
Dutasteride	0	0	0	0		no	
Efavirenz	0	0	0	1		yes	
Emtricitabine	0	0	0	0		yes	
Enalapril	0	0	0	0		yes	
Enoxaparin	0	0	3	0		no	
Entacapone	0	0	0	0		yes	
Enzalutamide	0	0	0	2		yes	
Ephedrine	0	0	0	0		no	
Epinephrine	0	0	3	0		no	
Epirubicin	0	0	0	1		yes	
Eplerenone	0	0	0	0		no	
Erenumab	0	0	0	0		no	
Ergocalciferol	0	0	9	0		no	

Erlotinib	0	0	0	1		yes	
Erythromycin	0	1	6	0		yes	
Erythropoietin	0	0	1	0		-	
Escitalopram	0	0	18	2		yes	
Eslicarbazepine	0	0	0	2	yes	yes	
Esomeprazole	0	3	33	1		yes	no
Estradiol	0	0	3	1		no	
Eszopiclone	0	0	2	1		yes	
Etanercept	0	0	0	0		no	
Ethambutol	0	0	0	0		yes	
Ethanol	0	0	0	0	yes / yes	yes	
Etoposide	0	0	0	0		no	
Everolimus	0	1	14	2		no	
Evolocumab	0	0	0	0		no	
Ezetimibe	0	0	0	1		no	
Famciclovir	0	0	0	0		no	
Famotidine	0	1	20	0		no	
Febuxostat	0	0	0	0		yes	
Felodipine	0	0	0	1		no	
Fenfluramine	0	0	1	0		no	
Fenofibrate	0	0	1	1		yes	
Fentanyl	0	0	1	3	no	yes	
Ferrous Gluconate	0	0	0	0		no	
Ferrous Sulfate Anhydrous	0	0	0	0		no	
Fexofenadine	0	0	15	2		no	
Finasteride	0	0	4	0		no	
Fingolimod	0	0	0	0		yes	
Fish Oil	0	1	17	0		no	
Fluconazole	0	0	6	0		yes	
Fludarabine	0	0	0	0		no	
Fludrocortisone	0	0	1	0		no	
Flunitrazepam	0	0	0	0		-	
Fluorouracil	0	0	0	1		no	
Fluoxetine	0	1	18	1		yes	
Flupentixol	0	0	0	0		-	
Flurazepam	0	0	0	0		yes	
Fluticasone	0	1	69	1		no	yes
Fluticasone Propionate	0	3	69	1		no	yes
Folic Acid	0	3	46	0		no	yes
Formoterol	0	0	3	1		no	
Fosamprenavir	0	0	0	0		yes	
Fosaprepitant	0	0	0	1		yes	
Fosinopril	0	0	0	0		yes	
Furosemide	0	0	8	0		no	
Gabapentin	0	2	70	0		yes	no
Gabapentin Enacarbil	0	0	0	0		yes	
Garlic	0	0	0	0		no	

Gemcitabine	0	0	0	2		yes	
Gemfibrozil	0	0	1	0		no	
Glatiramer	0	0	0	0		no	
Glecaprevir	0	0	0	1		no	
Glimepiride	0	0	0	1		no	
Glipizide	0	0	1	1		no	
Glucosamine	0	0	2	0		no	
Glyburide	0	0	0	0		no	
Gold	0	0	0	0		-	
Granisetron	0	0	0	1		no	
Guaifenesin	0	0	6	0		no	
Haloperidol	0	0	4	2		yes	
Heparin	0	0	1	0		no	
Hesperidin	0	0	0	0		-	
Human Interferon Beta	0	0	0	0		-	
Hyaluronic Acid	0	0	0	0		-	
Hydralazine	0	0	3	0		no	
Hydrochlorothiazide	0	0	8	0		no	
Hydrocodone	0	0	2	2		yes	
Hydrocortisone	0	0	11	0		no	
Hydromorphone	0	0	0	1		yes	
Hydroxychloroquine	0	0	3	0		no	
Hydroxyzine	0	0	9	0		yes	
Hyoscyamine	0	0	3	0		no	
Ibandronate	0	0	0	0		no	
Ibuprofen	0	3	56	0		yes	no
Imatinib	0	0	0	2		yes	
Imidazole Salicylate	0	0	0	0		-	
Indapamide	0	0	0	2		no	
Infliximab	0	0	0	0		yes	
Influenza Virus Vaccine	0	0	1	0		no	
Insulin Aspart	0	0	3	0		no	
Insulin Detemir	0	0	0	0		no	
Insulin Glargine	0	0	4	0		no	
Insulin Human	0	0	0	0		no	
Insulin Lispro	0	0	1	0		no	
Interferon alfa-n1	0	0	0	0		yes	
Interferon beta-1a	0	0	0	0		yes	
Interferon beta-1b	0	0	0	0		yes	
Ipilimumab	0	0	0	0		yes	
Ipratropium	0	1	24	0		no	
Irbesartan	0	0	0	1		no	
Iron	0	0	14	0		no	
Isosorbide Dinitrate	0	0	2	0		no	
Isosorbide Mononitrate	0	0	0	1		no	
Isotretinoin	0	0	0	0		yes	
Keratin	0	0	0	0		-	

Ketoconazole	0	0	2	0	yes	yes	
Krill Oil	0	0	0	0		no	
Labetalol	0	0	0	1		yes	
Lacosamide	0	16	350	1	no	no	no
Lactic Acid	0	0	0	0		no	
Lactobacillus Acidophilus	0	0	0	0		no	
Lactulose	0	1	16	0		no	
Lamivudine	0	0	0	2		yes	
Lamotrigine	0	16	392	0	no	yes	no
Lanreotide	0	0	0	0		no	
Lansoprazole	0	1	36	0		yes	
Lapatinib	0	0	0	1		yes	
Latanoprost	0	0	2	0		no	
Lavender Oil	0	0	0	0		no	
Ledipasvir	0	0	0	0		no	
Leflunomide	0	0	0	0		yes	
Lenalidomide	0	0	0	3		yes	
Lenvatinib	0	0	0	2		yes	
Letrozole	0	0	0	2		yes	
Leucovorin	0	0	4	0		no	
Levetiracetam	0	19	487	3	no / no	yes	no
Levodopa	0	0	7	0		no	
Levofloxacin	0	0	4	0		yes	
Levomefolic Acid	0	1	2	0		no	
Levosalbutamol	0	0	7	1		-	
Levothyroxine	0	2	67	0		no	yes
Lidocaine	0	0	6	0		no	
Linagliptin	0	0	0	0		no	
Linezolid	0	0	0	0		no	
Liothyronine	0	0	1	0		no	
Liotrix	0	0	0	0		no	
Lisinopril	0	0	11	0		yes	
Lithium Aspartate	0	0	1	0		-	
Lithium Carbonate	0	0	0	0		yes	
Loperamide	0	0	4	0		no	
Loratadine	0	6	34	2		no	
Lorazepam	0	6	137	2		yes	no
Losartan	0	0	7	2		no	
Lovastatin	0	0	1	2		yes	
Loxapine	0	0	0	0		yes	
Lubiprostone	0	0	1	0		no	
Lurasidone	0	0	1	3		yes	
Lysergic Acid Diethylamide	0	0	0	0		-	
Magnesium	0	0	17	0		no	
Magnesium Aspartate	0	0	0	0		no	
Magnesium Chloride	0	0	0	0		no	
Magnesium Hydroxide	0	0	10	0		no	

Magnesium Oxide	0	0	7	0		no	
Meclizine	0	0	1	1		yes	
Megestrol Acetate	0	0	3	1		no	
Melatonin	0	3	104	0		no	yes
Meloxicam	0	0	10	2		yes	
Memantine	0	0	2	2		no	
Menthol	0	0	0	0		no	
Meperidine	0	0	0	0		yes	
Meprobamate	0	0	0	0		yes	
Mesalazine	0	0	2	0		-	
Metamizole	0	0	0	0		-	
Metformin	0	0	10	0	yes	no	
Methadone	0	0	1	0		yes	
Methamphetamine	0	0	0	0		no	
Methocarbamol	0	0	0	0		yes	
Methotrexate	0	0	1	0		yes	
Methotrimeprazine	0	0	0	0		yes	
Methsuximide	0	0	0	1		yes	
Methylpyrrolidone	0	0	0	0		-	
Methylcellulose	0	0	0	0		no	
Methylcobalamin	0	0	0	0		no	
Methylphenidate	0	0	18	2		no	
Methylprednisolone	0	0	2	0		no	
Methyltestosterone	0	0	0	0		yes	
Metoclopramide	0	1	9	1		yes	
Metolazone	0	0	0	0		no	
Metoprolol	0	0	9	1		no	
Metronidazole	0	0	1	1		no	
Midodrine	0	0	5	0		no	
Midomafetamine	0	0	0	0		-	
Minocycline	0	0	2	0		yes	
Mirtazapine	0	0	10	2		yes	
Modafinil	0	0	0	2		no	
Mometasone	0	0	10	1		no	
Mometasone Furoate	0	0	10	1		no	
Montelukast	0	4	55	1		no	yes
Morphine	0	0	2	1		yes	
Moxifloxacin	0	0	0	0		yes	
Mycophenolic Acid	0	0	0	3		no	
Nabumetone	0	0	0	0		yes	
Naldemedine	0	0	0	0		no	
Naloxone	0	0	0	0		no	
Naltrexone	0	0	2	0		yes	
Naphazoline	0	0	0	0		no	
Naproxen	0	0	1	2		yes	
Nebivolol	0	0	0	0		no	
Nevirapine	0	0	0	0		yes	

Niacin	0	0	1	0		yes	
Niacinamide	0	0	0	0		yes	
Nicardipine	0	0	0	1		no	
Nicotine	0	0	0	0		no	
Nifedipine	0	0	0	2		no	
Nitrofurantoin	0	0	7	0		yes	
Nitroglycerin	0	0	1	0		no	
Nivolumab	0	0	0	0		no	
Nordazepam	0	0	0	0		-	
Norepinephrine	0	0	0	0		no	
Nortriptyline	0	0	4	0		yes	
Nystatin	0	0	20	0		no	
Ocrelizumab	0	0	0	0		no	
Octreotide	0	0	0	2		no	
Olanzapine	0	0	9	3		yes	
Olopatadine	0	0	2	2		yes	
Ombitasvir	0	0	0	2		no	
Omega-3 Fatty Acids	0	0	3	0		no	
Omega-6 Fatty Acids	0	0	0	0		-	
Omeprazole	0	0	62	1	no	yes	yes
Ondansetron	0	2	28	1		no	
Opipramol	0	0	0	0		-	
Orphenadrine	0	0	0	0		yes	
Osimertinib	0	0	0	2		no	
Oxaliplatin	0	0	0	0		yes	
Oxazepam	0	0	0	0		yes	
Oxcarbazepine	0	1	101	3	no	yes	yes
Oxybutynin	0	0	2	3		no	
Oxycodone	0	0	5	3		yes	
Oxymorphone	0	0	0	2		yes	
Oxyquinoline	0	0	0	0		-	
Paclitaxel	0	0	0	1		no	
Palbociclib	0	0	0	1		no	
Paliperidone	0	0	0	2		yes	
Palonosetron	0	0	0	0		no	
Pancrelipase Amylase	0	0	0	0		no	
Pancrelipase Lipase	0	0	0	0		no	
Pancrelipase Protease	0	0	0	0		no	
Pantoprazole	0	1	14	1		no	
Pantothenic Acid	0	0	0	0		-	
Paritaprevir	0	0	0	2		no	
Paroxetine	0	0	7	3		yes	
Peginterferon alfa-2a	0	0	0	0		yes	
Peginterferon alfa-2b	0	0	0	3		yes	
Pembrolizumab	0	0	0	0		no	
Pemetrexed	0	0	0	0		no	
Pentamidine	0	0	0	2		no	

Pentazocine	0	0	0	0		yes	
Perampanel	0	6	11	2	no	yes	no
Perindopril	0	0	0	0		yes	
Phencyclidine	0	0	0	0		no	
Pheniramine	0	0	0	0		no	
Phenobarbital	0	6	114	0	no	yes	no
Phenoxymethylpenicillin	0	0	0	0		-	
Phentermine	0	0	1	0		no	
Phenylbutazone	0	0	0	0		yes	
Phenytoin	0	5	60	1	no	yes	yes
Pibrentasvir	0	0	0	1		no	
Pipamperone	0	0	0	0		-	
Piracetam	0	0	0	0		-	
Pirfenidone	0	0	0	3		yes	
Piritramide	0	0	0	0		-	
Piroxicam	0	0	1	0		yes	
Polyethylene Glycol	0	7	116	0		no	yes
Posaconazole	0	0	0	3		yes	
Potassium	0	0	6	0		-	
Potassium Chloride	0	0	18	0		no	
Pramipexole	0	0	2	0		yes	
Prasterone	0	0	0	0		yes	
Prasugrel	0	0	0	0		no	
Pravastatin	0	0	7	1		yes	
Prazosin	0	0	0	0		no	
Prednisolone	0	0	10	0		no	
Prednisone	0	2	16	0		no	
Pregabalin	0	0	6	0	no	yes	
Primidone	0	1	12	0		yes	
Procarbazine	0	0	0	0		no	
Prochlorperazine	0	0	0	0		yes	
Procyclidine	0	0	0	0		yes	
Progesterone	0	0	3	2		no	
Promethazine	0	0	2	0		yes	
Propafenone	0	0	0	1		no	
Propiverine	0	0	0	0		-	
Propranolol	0	0	13	0		no	
Propyphenazone	0	0	0	0		-	
Prothipendyl	0	0	0	0		-	
Prucalopride	0	0	3	0		no	
Pseudoephedrine	0	0	2	0		no	
Psyllium (Plantago Seed)	0	0	0	0		no	
Pyridoxine	0	0	11	0		no	
Pyrimethamine	0	0	0	0		no	
Quetiapine	0	0	27	3		yes	
Quinapril	0	0	0	0		yes	
Quinidine	0	0	1	1		no	

Quinine	0	0	0	1		no	
Rabeprazole	0	0	0	1		no	
Raloxifene	0	0	0	1		no	
Ramipril	0	0	0	0		yes	
Ranitidine	0	1	56	2		no	yes
Repaglinide	0	0	0	1		no	
Ribavirin	0	0	0	0		no	
Riboflavin	0	0	2	0		no	
Rifampicin	0	0	0	0	yes	yes	
Rimantadine	0	0	0	0		no	
Riociguat	0	0	0	1		no	
Risedronic Acid	0	0	2	0		no	
Risperidone	0	2	52	3		yes	yes
Ritonavir	0	0	0	2		yes	
Rituximab	0	0	0	0		no	
Rivaroxaban	0	0	1	0		no	
Rivastigmine	0	0	0	0		no	
Rofecoxib	0	0	0	2		yes	
Ropinirole	0	0	3	3		yes	
Rosiglitazone	0	0	0	1		yes	
Rosuvastatin	0	0	2	0		yes	
Rucaparib	0	0	0	3		no	
Salbutamol	0	1	36	2		no	
Salicylic Acid	0	0	0	0		no	
Salmeterol	0	0	13	1		no	
Sargramostim	0	0	0	0		no	
Scopolamine	0	3	6	0		no	
Selegiline	0	0	0	3		no	
Sennosides	0	0	17	0		no	
Serine	0	0	0	0		-	
Serrapeptase	0	0	0	0		-	
Sertraline	0	0	36	1		yes	
Sevelamer	0	1	0	0		no	
Sildenafil	0	0	1	1		no	
Silodosin	0	0	0	1		no	
Simvastatin	0	0	7	1		yes	
Sipuleucel-T	0	0	0	0		no	
Sitagliptin	0	0	0	1		no	
Sodium Aurothiomalate	0	0	0	0		no	
Sodium Bicarbonate	0	0	2	0		no	
Sodium Chloride	0	0	31	0		no	
Sodium Citrate	0	0	1	0		no	
Sodium Lauryl Sulfoacetate	0	0	0	0		-	
Sodium Oxybate	0	0	0	0		no	
Sofosbuvir	0	0	0	1		no	
Sorafenib	0	0	0	2		yes	
Sorbitol	0	0	0	0		no	

Sotalol	0	0	1	3		no	
Spironolactone	0	0	6	0		no	
Stavudine	0	0	0	0		yes	
Sucralfate	0	0	1	0		no	
Sulbactam	0	0	0	0		no	
Sulfamethoxazole	0	1	3	0		yes	
Sulfasalazine	0	0	0	0	yes	yes	
Sulpiride	0	0	0	0		-	
Sumatriptan	0	0	4	2		no	
Sunitinib	0	0	0	3		yes	
Tacrolimus	0	1	3	3		no	
Tadalafil	0	0	1	1		no	
Tamsulosin	0	0	6	2		no	
Tapentadol	0	0	0	3		yes	
Tegaserod	0	0	0	1		no	
Telaprevir	0	0	0	1		yes	
Telmisartan	0	0	1	1		no	
Temazepam	0	0	3	1		yes	
Tenofovir	0	0	0	1		yes	
Terazosin	0	0	0	0		no	
Terbinafine	0	0	0	1		yes	
Teriflunomide	0	0	0	0		yes	
Teriparatide	0	0	0	0		no	
Testosterone	0	0	0	1		yes	
Testosterone Undecanoate	0	0	0	1		yes	
Theophylline	0	0	0	0		no	
Thiamine	0	0	3	0		no	
Timolol	0	0	3	0		no	
Tiotropium	0	0	1	1		no	
Tizanidine	0	0	7	2		yes	
Tobacco Leaf	0	0	0	0		-	
Tocilizumab	0	0	1	1		yes	
Tofacitinib	0	0	0	1		no	
Tolterodine	0	0	0	1		no	
Topiramate	0	4	247	2	no / yes	yes	no
Topotecan	0	0	0	2		no	
Torasemide	0	0	0	1		no	
Tramadol	0	0	0	3		yes	
Trazodone	0	2	30	2		yes	
Triamcinolone	0	0	11	0		no	
Triamterene	0	0	1	0		no	
Triazolam	0	0	0	1		yes	
Trimebutine	0	0	0	0		-	
Trimethoprim	0	1	11	0		no	
Trospium	0	0	0	1		no	
Turmeric	0	0	0	0		no	
Ubidecarenone	0	0	5	0		-	

Urelumab	0	0	0	0		-	
Ustekinumab	0	0	0	0		no	
Valproic Acid	0	7	292	2	no / no / no	yes	no
Valsartan	0	0	0	1		no	
Vancomycin	0	2	2	0		no	
Varenicline	0	0	0	0		no	
Vedolizumab	0	0	0	0		no	
Velpatasvir	0	0	0	2		no	
Vemurafenib	0	0	0	3		yes	
Venetoclax	0	0	0	3		no	
Venlafaxine	0	0	9	3		yes	
Verapamil	0	1	1	1	yes	yes	
Vilanterol	0	0	0	1		no	
Vincristine	0	0	0	0	yes	yes	
Vindesine	0	0	0	0		-	
Vismodegib	0	0	0	1		no	
Vitamin B12	0	0	34	0		no	
Vitamin D	0	3	168	0		no	yes
Vitamin E	0	0	14	0		no	
Warfarin	0	0	2	0	yes	yes	
Zidovudine	0	0	0	1		yes	
Ziprasidone	0	0	4	1		yes	
Zolpidem	0	0	4	2		yes	
Zonisamide	0	3	128	1	yes	yes	no
Zopiclone	0	0	0	0		no	
Zuclopenthixol	0	0	0	0		-	

Table 36. List with Interesting Drugs that might Interact with THC. *Column 1: Drugs; Column 2: Number of reports from people over or equal 50 years old that contain this drug; Column 3: Number of reports from people under 50 years old that contain this drug; Column 4: Number of reports from people with no defined age that contain this drug; Column 5: Prediction of correlation in between pharmacokinetic and pharmacodynamic interaction from 'PK-PD-Correlation' Table; Column 6: Known interactions from literature (no guarantee of completeness); Column 7: Interaction regarding 'Wechselwirkungscheck' on DocCheck and 'drug interactions checker' on drug.com (see 2.2.2.3 drug interactions); Column 8: Note, if drug might be interesting for further analysis or future studies; Colors: light red - over 1% frequency, dark red - over 10% frequency; Additional information e.g data sources, details about interaction etc. is available in Excel file 'List with Interesting Drugs'*

Drugs	# of reports ≥ 50 years	# of reports < 50 years	# of reports not defined age	Drug Interaction Prediction (# of correlation)	Known Interactions (Literature)	Interactions Checker	INTERESTING DRUGS
Abatacept	4	3	2	0		no	
Acetaminophen	22	113	21	1		no	no
Acetylcysteine	0	0	0	0		no	
Acyclovir	8	6	8	0		no	
Adalimumab	2	2	3	0		no	
Alendronic Acid	0	0	1	0		no	
Alfuzosin	0	0	1	1		yes	
Alimemazine	0	12	0	0		-	
Alizapride	2	0	0	0		no	
Allopurinol	2	5	0	0		no	
Alprazolam	16	81	12	1		yes	no
Amantadine	22	0	8	0		no	no
Aminosalicylic Acid	2	0	0	0		no	
Amiodarone	2	0	0	1		no	
Amisulpride	9	8	0	0		no	no
Amitriptyline	43	25	26	2		yes	no
Amlodipine	15	2	2	1		yes	no
Amoxapine	1	0	0	1		yes	
Amoxicillin	1	2	0	0		no	
Amphetamine	2	70	3	3		no	no
Ampicillin	16	0	0	0		no	yes
Anakinra	0	0	0	0		no	
Apixaban	1	0	0	0		no	
Apremilast	0	1	0	2		no	
Aprepitant	6	3	2	1		yes	no
Aripiprazole	11	6	0	1		yes	no
Armodafinil	0	0	0	1		yes	
Arnica Montana Flower	0	0	0	0		no	
Ascorbic Acid	14	10	2	0		no	
Aspirin	39	18	9	0		no	yes
Atenolol	5	6	3	2		yes	
Atorvastatin	13	1	1	1		no	yes
Atropine	3	1	0	0		no	
Avelumab	1	0	0	0		no	
Azithromycin	1	4	1	1		no	
Baclofen	24	14	10	0		yes	no
Beclomethasone Dipropionate	1	0	0	1		no	

Benazepril	4	0	1	0		yes	
Benperidol	9	0	0	0		-	yes
Benzatropine	0	0	0	0		-	
Benzodiazepine	0	14	2	0		-	no
Benzoylecgonine	2	9	2	0		-	no
Bevacizumab	2	0	0	0		no	
Bictegravir	0	0	0	1		no	
Biotin	3	0	0	0		no	
Bisacodyl	13	2	2	0		no	no
Bisoprolol	3	0	0	0		yes	
Bleomycin	5	3	0	0		no	
Boceprevir	1	0	0	1		no	
Bosentan	0	0	0	1		yes	
Brimonidine	0	0	0	0		yes	
Brinzolamide	0	0	0	0		no	
Brivanib Alaninate	1	0	0	0		-	
Brivaracetam	4	0	1	1		yes	
Bromazepam	10	1	0	1		-	yes
Budesonide	2	1	2	2		no	
Bumetanide	1	0	0	0		yes	
Bupivacaine	0	1	1	0		no	
Buprenorphine	7	87	13	1		yes	no
Bupropion	7	1	5	1		yes	
Buspirone	1	0	1	1		yes	
Butalbital	1	0	1	0		yes	
Caffeine	1	16	15	0		no	no
Calcium	6	3	3	0		no	
Calcium Carbonate	1	0	1	0		no	
Calcium Chloride	1	0	0	0		no	
Calcium Phosphate	7	0	0	0		no	
Canakinumab	0	0	0	0		no	
Candesartan	0	0	0	2		yes	
Carbamazepine	18	6	15	1		yes	no
Carbazochrome	0	0	0	0		-	
Carbidopa	21	1	8	0		no	no
Carboplatin	3	1	1	0		no	
Carboxymethylcellulose	0	0	0	0		no	
Cariprazine	1	0	0	1		yes	
Carisoprodol	5	26	4	1		yes	no
Carvedilol	4	0	2	2		yes	
Cefaclor	0	0	0	0		no	
Cefepime	2	0	0	0		no	
Ceftriaxone	0	0	0	0		no	
Cefuroxime	1	0	1	0		no	
Celecoxib	2	3	15	1		no	
Cephalexin	0	1	0	0		no	
Cetirizine	4	0	0	1		yes	
Cetuximab	5	0	0	0		no	

Chlordiazepoxide	0	2	0	0		yes	
Chlorpromazine	10	6	0	1		yes	no
Chlorthalidone	0	0	0	0		yes	
Cholecalciferol	0	0	0	0		no	
Cholestyramine	1	1	0	0		no	
Chondroitin Sulfate	1	0	0	0		no	
Cilostazol	1	0	0	1		no	
Ciprofloxacin	5	2	1	1		no	
Cisplatin	32	13	0	0		no	yes
Citalopram	2	64	4	1		yes	no
Citicoline	0	0	0	0		no	
Citric Acid	7	1	0	0		no	yes
Clavulanic Acid	1	0	0	0		no	
Clindamycin	1	2	0	0		no	
Clobetasol	0	0	0	0		no	
Clobetasol Propionate	0	0	0	0		no	
Clonazepam	18	68	14	1		yes	no
Clonidine	12	1	9	2		yes	no
Clopidogrel	6	0	0	0		no	
Clotrimazole	1	0	0	0		no	
Clozapine	26	18	9	2	no	yes	yes
Cobalamin	0	0	0	0		no	
Cobimetinib	6	0	0	1		no	
Cocaine	2	62	5	1		no	no
Codeine	2	68	20	1		yes	no
Colchicine	0	2	0	0		no	
Colestipol	1	0	0	0		no	
Collagen	1	0	0	0		no	
Conjugated Estrogens	0	0	0	1		no	
Corticotropin	0	0	0	3		no	
Cortisone Acetate	0	1	0	1		no	
Crizotinib	2	4	0	3		no	
Curcumin	0	0	0	0		-	
Cyclizine	2	2	0	0		yes	
Cyclobenzaprine	1	8	2	0		yes	
Cyclophosphamide	33	21	8	0		no	yes
Cyclosporine	2	1	0	3		no	
Dabigatran Etexilate	1	0	0	0		no	
Daclatasvir	0	0	0	0		no	
Dalfampridine	0	0	0	0		no	
Dantrolene	2	1	0	0		yes	
Danvatirsen	0	0	0	0		-	
Daprodustat	4	0	0	0		-	
Darbepoetin Alfa	11	0	0	0		no	yes
Darunavir	0	6	2	0		no	
Dasabuvir	0	0	0	1		no	
Dasatinib	3	0	0	3		no	
Deflazacort	3	0	0	2		no	

Denosumab	3	0	0	0		no	
Desloratadine	0	0	0	0		no	
Desmopressin	2	0	1	0		no	
Desvenlafaxine	0	0	0	1		yes	
Dexamethasone	31	5	2	0		no	yes
Dextroamphetamine	0	2	2	0		no	
Dextromethorphan	12	3	0	0	yes	yes	no
Dextropropoxyphene	1	4	1	0		-	
Diamorphine	2	38	2	0		-	no
Diazepam	23	133	24	1		yes	no
Diclofenac	5	2	1	0	yes	no	
Dicyclomine	1	1	1	0		no	
Digoxin	4	0	1	1		no	
Dihydrocodeine	2	8	0	1		yes	no
Diltiazem	3	0	2	1	yes	yes	
Dimenhydrinate	10	1	2	0		yes	no
Diosmin	1	0	0	0		-	
Diphenhydramine	8	23	5	0		yes	no
Diphenoxylate	2	0	0	0		yes	
Docusate	5	12	4	0		no	
Dofetilide	1	0	0	2		no	
Domperidone	6	4	2	0		-	
Donepezil	21	0	0	1		no	no
Dopamine	0	0	0	0		no	
Dorzolamide	1	0	0	0		no	
Doxazosin	1	0	0	1		yes	
Doxepin	5	8	1	0		yes	
Doxorubicin	32	17	8	1	no	no	yes
Doxycycline	0	1	0	1		no	
Droperidol	0	1	0	0		yes	
Duloxetine	65	35	17	1		yes	no
Durvalumab	0	0	0	0		no	
Dutasteride	0	0	0	0		no	
Efavirenz	1	3	0	1		yes	
Emtricitabine	1	7	0	0		no	
Enalapril	3	2	0	0		yes	
Enoxaparin	4	1	2	0		no	
Entacapone	21	0	8	0		yes	no
Enzalutamide	2	0	0	3		no	
Ephedrine	0	5	0	0		no	
Epinephrine	1	0	0	0		no	
Epirubicin	0	0	0	1		no	
Eplerenone	0	0	0	1		yes	
Erenumab	0	0	0	0		no	
Ergocalciferol	5	1	1	0		no	
Erlotinib	4	0	0	2		no	
Erythromycin	1	2	1	0		no	
Erythropoietin	5	0	1	0		-	

Escitalopram	9	16	4	1		yes	no
Eslicarbazepine	3	0	1	1		yes	
Esomeprazole	13	3	13	1		no	yes
Estradiol	1	1	1	0		no	
Eszopiclone	2	0	1	1		yes	
Etanercept	46	0	11	0		no	no
Ethambutol	0	0	1	0		no	
Ethanol	5	64	5	0		yes	no
Etoposide	26	8	8	1		no	yes
Everolimus	0	0	1	3		no	
Evolocumab	0	0	0	0		no	
Ezetimibe	1	0	0	0		no	
Famciclovir	0	4	0	0		no	
Famotidine	6	1	1	0		no	yes
Febuxostat	0	0	0	0		no	
Felodipine	0	0	0	1		yes	
Fenfluramine	1	0	0	0		no	
Fenofibrate	1	1	1	0		no	
Fentanyl	22	52	33	1		yes	no
Ferrous Gluconate	0	1	0	0		no	
Ferrous Sulfate Anhydrous	0	0	0	0		no	
Fexofenadine	1	0	0	1		no	
Finasteride	2	0	0	0		no	
Fingolimod	2	0	0	0		no	
Fish Oil	5	0	1	0		no	
Fluconazole	2	12	0	1		no	
Fludarabine	0	0	0	0		no	
Fludrocortisone	13	0	5	0		no	yes
Flunitrazepam	0	13	0	0		-	no
Fluorouracil	5	1	0	0		no	
Fluoxetine	6	12	5	1		yes	
Flupentixol	16	0	0	0		-	yes
Flurazepam	1	1	0	0		yes	
Fluticasone	5	1	4	1		no	
Fluticasone Propionate	2	1	4	1		no	
Folic Acid	5	4	2	0		no	
Formoterol	17	0	3	1		no	no
Fosamprenavir	0	0	0	0		no	
Fosaprepitant	0	0	0	1		yes	
Fosinopril	2	0	0	0		yes	
Furosemide	26	9	4	0		yes	no
Gabapentin	91	52	26	0	yes	yes	no
Gabapentin Enacarbil	0	0	0	0		yes	
Garlic	0	0	0	0		no	
Gemcitabine	3	0	1	3		no	
Gemfibrozil	0	0	1	1		no	
Glatiramer	0	0	0	0		no	

Glecaprevir	0	0	0	0		no	
Glimepiride	0	0	0	1		no	
Glipizide	11	1	1	1		no	yes
Glucosamine	2	0	0	0		no	
Glyburide	1	0	0	0		no	
Gold	0	0	0	0		-	
Granisetron	9	5	0	1		no	yes
Guaifenesin	1	0	0	0		no	
Haloperidol	3	4	4	1		yes	
Heparin	2	4	0	0		no	
Hesperidin	1	0	0	0		-	
Human Interferon Beta	0	0	0	0		-	
Hyaluronic Acid	0	0	0	0		-	
Hydralazine	1	0	0	0		yes	
Hydrochlorothiazide	5	1	2	0		yes	
Hydrocodone	15	46	14	1		yes	no
Hydrocortisone	1	4	0	0		no	
Hydromorphone	31	31	22	1		yes	no
Hydroxychloroquine	0	2	0	0		no	
Hydroxyzine	1	6	8	0		yes	
Hyoscyamine	2	1	0	0		no	
Ibandronate	5	0	0	0		no	
Ibuprofen	16	24	6	1		no	no
Imatinib	1	0	0	2		no	
Imidazole Salicylate	0	0	0	0		-	
Indapamide	2	0	0	1		yes	
Infliximab	3	1	0	0		no	
Influenza Virus Vaccine	1	0	0	0		no	
Insulin Aspart	0	1	0	0		no	
Insulin Detemir	0	0	0	0		no	
Insulin Glargine	2	2	0	0		no	
Insulin Human	1	0	0	0		no	
Insulin Lispro	2	1	0	0		no	
Interferon alfa-n1	0	0	0	0		no	
Interferon beta-1a	0	0	0	0		no	
Interferon beta-1b	0	0	0	0		no	
Ipilimumab	3	0	0	0		no	
Ipratropium	4	0	1	0		no	
Irbesartan	0	0	0	1		yes	
Iron	2	0	1	0		no	
Isosorbide Dinitrate	0	0	0	0		yes	
Isosorbide Mononitrate	0	0	1	1		yes	
Isotretinoin	3	0	0	0		no	
Keratin	1	0	0	0		-	
Ketoconazole	0	2	0	0	yes	no	
Krill Oil	0	0	0	0		no	
Labetalol	1	0	0	1		yes	
Lacosamide	2	0	0	1		no	

Lactic Acid	0	0	0	0		no	
Lactobacillus Acidophilus	0	0	1	0		no	
Lactulose	1	1	2	0		no	
Lamivudine	1	3	0	2		no	
Lamotrigine	6	4	10	0		yes	
Lanreotide	1	0	0	2		no	
Lansoprazole	2	3	4	1		no	
Lapatinib	0	0	0	1		yes	
Latanoprost	3	0	0	0		no	
Lavender Oil	2	0	0	0		no	
Ledipasvir	0	0	0	1		no	
Leflunomide	0	0	0	1		no	
Lenalidomide	2	0	1	2		no	
Lenvatinib	2	0	0	2		no	
Letrozole	2	0	0	1		no	
Leucovorin	5	1	0	0		no	
Levetiracetam	8	4	5	2		yes	
Levodopa	21	9	8	0		no	no
Levofloxacin	8	1	3	1		no	
Levomefolic Acid	0	0	0	0		no	
Levosalbutamol	1	0	1	1		-	
Levothyroxine	22	1	7	0		no	yes
Lidocaine	3	21	1	0		no	no
Linagliptin	0	0	0	0		no	
Linezolid	1	0	0	0		no	
Liothyronine	3	0	0	0		no	
Liotrix	1	0	0	0		no	
Lisinopril	11	7	5	0		yes	
Lithium Aspartate	0	0	0	0		-	
Lithium Carbonate	1	0	0	0		yes	
Loperamide	15	6	3	1		no	no
Loratadine	1	5	2	0		no	
Lorazepam	88	43	27	1		yes	yes
Losartan	4	0	2	1		yes	
Lovastatin	2	1	1	0		no	
Loxapine	0	0	0	0		yes	
Lubiprostone	2	1	0	0		no	
Lurasidone	0	0	0	2		yes	
Lysergic Acid Diethylamide	0	0	0	0		-	
Magnesium	12	0	0	0		no	yes
Magnesium Aspartate	0	0	0	0		no	
Magnesium Chloride	1	0	0	0		no	
Magnesium Hydroxide	1	0	1	0		no	
Magnesium Oxide	2	1	0	0		no	
Meclizine	0	2	0	0		yes	
Megestrol Acetate	14	1	3	1		no	
Melatonin	1	5	1	1		no	

Meloxicam	0	1	0	1		no	
Memantine	5	0	0	0		no	
Menthol	0	0	0	0		no	
Meperidine	1	12	0	0		yes	no
Meprobamate	1	5	1	0		yes	
Mesalazine	3	1	0	0		-	
Metamizole	9	0	0	0		-	yes
Metformin	14	2	3	0		no	yes
Methadone	2	132	15	0		yes	no
Methamphetamine	3	44	7	0		no	no
Methocarbamol	2	3	1	0		yes	
Methotrexate	0	7	0	1		no	
Methotrimeprazine	2	0	0	0		yes	
Methsuximide	0	0	0	1		yes	
Methylpyrrolidone	0	0	0	0		-	
Methylcellulose	0	0	0	0		no	
Methylcobalamin	0	0	0	0		no	
Methylphenidate	3	13	0	1		no	no
Methylprednisolone	4	2	1	0		no	
Methyltestosterone	0	0	0	0		no	
Metoclopramide	40	14	8	0		yes	no
Metolazone	1	0	0	0		yes	
Metoprolol	12	5	7	1		yes	no
Metronidazole	2	3	1	1		no	
Midodrine	1	1	0	1		no	
Midomafetamine	0	33	1	0		-	no
Minocycline	0	1	0	0		no	
Mirtazapine	23	26	4	1		yes	no
Modafinil	0	1	1	1		yes	
Mometasone	2	4	3	1		no	
Mometasone Furoate	2	4	3	1		no	
Montelukast	3	1	3	1		no	
Morphine	29	129	8	1		yes	no
Moxifloxacin	0	0	0	0		no	
Mycophenolic Acid	0	0	0	0		no	
Nabumetone	1	0	0	1		no	
Naldemedine	1	0	0	0		no	
Naloxone	10	16	8	0		no	no
Naltrexone	0	0	1	0		no	
Naphazoline	0	0	0	0		no	
Naproxen	4	13	1	1		no	no
Nebivolol	0	0	0	1		yes	
Nevirapine	2	0	0	0		no	
Niacin	0	0	0	0		no	
Niacinamide	0	0	0	0		no	
Nicardipine	0	0	0	1		yes	
Nicotine	0	17	3	1		no	no
Nifedipine	12	0	2	1		yes	no

Nitrofurantoin	1	1	1	0		no	
Nitroglycerin	4	0	0	0		yes	
Nivolumab	1	0	1	0		no	
Nordazepam	1	38	1	0		-	no
Norepinephrine	0	1	0	0		no	
Nortriptyline	6	6	6	0		yes	
Nystatin	2	5	0	0		no	
Ocrelizumab	1	0	0	0		no	
Octreotide	1	0	1	2		no	
Olanzapine	10	47	6	1		yes	no
Olopatadine	0	0	0	1		yes	
Ombitasvir	0	0	0	1		no	
Omega-3 Fatty Acids	0	0	0	0		no	
Omega-6 Fatty Acids	0	0	0	0		-	
Omeprazole	14	12	8	1	no	no	yes
Ondansetron	43	21	8	1		no	yes
Opipramol	2	0	0	0		-	
Orphenadrine	0	0	0	0		yes	
Osimertinib	0	0	0	0		no	
Oxaliplatin	5	0	0	0		no	
Oxazepam	9	36	3	0		yes	no
Oxcarbazepine	2	1	1	1		yes	
Oxybutynin	1	1	0	1		no	
Oxycodone	22	151	34	1		yes	no
Oxymorphone	1	17	5	1		yes	no
Oxyquinoline	0	0	0	0		-	
Paclitaxel	2	0	0	2		no	
Palbociclib	1	0	2	1		no	
Paliperidone	0	1	0	1		yes	
Palonosetron	1	1	0	1		no	
Pancrelipase Amylase	2	0	0	0		no	
Pancrelipase Lipase	2	0	0	0		no	
Pancrelipase Protease	2	0	0	0		no	
Pantoprazole	64	14	8	1		no	yes
Pantothenic Acid	0	0	0	0		-	
Paritaprevir	0	0	0	1		no	
Paroxetine	17	18	1	1		yes	no
Peginterferon alfa-2a	0	1	0	0		no	
Peginterferon alfa-2b	1	0	0	1		no	
Pembrolizumab	1	1	0	0		no	
Pemetrexed	0	1	0	0		no	
Pentamidine	8	2	0	1		no	yes
Pentazocine	0	0	0	1		yes	
Perampanel	4	0	2	1		yes	
Perindopril	2	0	0	0		yes	
Phencyclidine	1	3	2	0		no	
Pheniramine	0	0	0	0		no	
Phenobarbital	2	9	2	0		yes	no

Phenoxymethylpenicillin	1	0	0	0		-	
Phentermine	1	0	0	1		no	
Phenylbutazone	2	0	0	0		no	
Phenytoin	2	4	1	1	yes	yes	
Pibrentasvir	0	0	0	1		no	
Pipamperone	11	0	0	0		-	yes
Piracetam	2	0	2	0		-	
Pirfenidone	0	0	0	2		no	
Piritramide	10	0	0	0		-	no
Piroxicam	2	0	0	1		no	
Polyethylene Glycol	10	5	3	0		no	
Posaconazole	0	0	0	3		no	
Potassium	6	1	1	0		-	
Potassium Chloride	10	2	3	0		no	
Pramipexole	21	2	8	0		yes	no
Prasterone	0	0	0	0		no	
Prasugrel	0	0	0	1		no	
Pravastatin	2	2	0	1		no	
Prazosin	0	1	1	1		yes	
Prednisolone	5	0	1	0		no	
Prednisone	9	5	6	0		no	yes
Pregabalin	19	26	8	0		yes	no
Primidone	1	0	1	0		yes	
Procarbazine	5	1	0	0		no	
Prochlorperazine	13	3	4	0		yes	no
Procyclidine	1	0	0	0		yes	
Progesterone	0	0	0	1		no	
Promethazine	13	31	7	0		yes	no
Propafenone	1	0	0	1		no	
Propiverine	1	0	0	0		-	
Propranolol	11	5	1	0		yes	no
Propyphenazone	1	0	0	0		-	
Prothipendyl	2	0	0	0		-	
Prucalopride	2	0	2	1		no	
Pseudoephedrine	2	8	0	0		no	
Psyllium (Plantago Seed)	0	0	0	0		no	
Pyridoxine	1	0	1	0		no	
Pyrimethamine	1	1	0	0		no	
Quetiapine	40	32	10	2		yes	yes
Quinapril	1	0	0	1		yes	
Quinidine	1	0	0	1		no	
Quinine	24	1	1	1		no	yes
Rabeprazole	5	1	1	1		no	
Raloxifene	1	0	0	2		no	
Ramipril	2	1	0	0		yes	
Ranitidine	6	5	2	1		no	
Repaglinide	5	0	0	0		no	

Ribavirin	1	1	2	0		no	
Riboflavin	0	0	1	0		no	
Rifampicin	0	0	1	0	yes	no	
Rimantadine	1	0	0	0		no	
Riociguat	0	0	0	1		no	
Risedronic Acid	0	0	0	0		no	
Risperidone	16	14	1	1	yes	yes	yes
Ritonavir	0	9	1	1		yes	
Rituximab	3	0	0	0		no	
Rivaroxaban	1	0	1	1		no	
Rivastigmine	19	0	0	0		no	no
Rofecoxib	1	1	0	1		no	
Ropinirole	0	1	1	2		yes	
Rosiglitazone	0	0	0	0		no	
Rosuvastatin	6	1	4	1		no	no
Rucaparib	0	0	0	2		yes	
Salbutamol	5	3	1	2		no	no
Salicylic Acid	0	0	0	0		no	
Salmeterol	4	1	1	1		no	
Sargramostim	8	0	0	0		no	yes
Scopolamine	7	7	0	0		no	
Selegiline	0	0	0	1		no	
Sennosides	6	4	2	0		no	
Serine	1	0	0	0		-	
Serrapeptase	0	0	0	0		-	
Sertraline	20	19	6	1		yes	no
Sevelamer	0	0	0	0		no	
Sildenafil	2	2	1	1		no	
Silodosin	1	0	0	1		yes	
Simvastatin	10	3	1	0		no	no
Sipuleucel-T	0	0	0	0		no	
Sitagliptin	4	0	0	0		no	
Sodium Aurothiomalate	0	0	0	0		no	
Sodium Bicarbonate	10	0	0	0		no	yes
Sodium Chloride	8	0	2	0		no	yes
Sodium Citrate	0	0	0	0		no	
Sodium Lauryl Sulfoacetate	0	0	0	0		-	
Sodium Oxybate	0	7	1	0		no	
Sofosbuvir	0	0	0	1		no	
Sorafenib	1	0	0	2		no	
Sorbitol	0	0	0	0		no	
Sotalol	1	0	0	1		yes	
Spironolactone	15	1	0	0		yes	yes
Stavudine	2	2	0	0		no	
Sucralfate	2	0	1	0		no	
Sulbactam	14	0	0	0		no	yes
Sulfamethoxazole	2	5	0	0		no	

Sulfasalazine	0	0	0	0	yes	no	
Sulpiride	2	0	0	0		-	
Sumatriptan	1	2	2	1		no	
Sunitinib	1	0	0	2		no	
Tacrolimus	9	1	0	2		yes	yes
Tadalafil	1	0	1	2		no	
Tamsulosin	5	3	0	2		yes	
Tapentadol	1	1	0	1		yes	
Tegaserod	1	0	0	1		no	
Telaprevir	0	1	0	1		no	
Telmisartan	2	0	0	0		yes	
Temazepam	5	28	3	1		yes	no
Tenofovir	1	8	0	1		no	no
Terazosin	2	0	0	0		yes	
Terbinafine	0	0	0	0		no	
Teriflunomide	1	0	0	0		no	
Teriparatide	1	0	0	0		no	
Testosterone	2	10	4	1		no	no
Testosterone Undecanoate	1	0	1	1		no	
Theophylline	2	1	0	0		yes	
Thiamine	0	0	1	0		no	
Timolol	2	0	0	1		yes	
Tiotropium	22	1	2	2		no	no
Tizanidine	3	3	8	2		yes	
Tobacco Leaf	0	0	0	0		-	
Tocilizumab	0	0	0	1		no	
Tofacitinib	0	0	1	1		no	
Tolterodine	1	2	1	1		no	
Topiramate	6	4	7	2		yes	
Topotecan	2	4	0	2		no	
Torasemide	0	0	0	0		yes	
Tramadol	47	54	16	1		yes	no
Trazodone	15	7	6	1		yes	no
Triamcinolone	1	2	0	0		no	
Triamterene	1	0	1	0		yes	
Triazolam	1	0	1	1		yes	
Trimebutine	0	0	0	1		-	
Trimethoprim	11	8	2	0		no	yes
Trospium	0	0	0	0		no	
Turmeric	0	0	0	0		no	
Ubidecarenone	0	0	2	0		-	
Urelumab	0	0	0	0		-	
Ustekinumab	1	0	0	0		no	
Valproic Acid	6	8	4	2		yes	
Valsartan	1	0	0	1		yes	
Vancomycin	0	0	0	0		no	
Varenicline	0	1	6	0		no	

Vedolizumab	1	0	0	0		no	
Velpatasvir	0	0	0	1		no	
Vemurafenib	7	1	0	3		no	yes
Venetoclax	1	0	0	2		no	
Venlafaxine	8	24	5	1		yes	no
Verapamil	1	1	0	1	no	yes	
Vilanterol	0	0	0	0		no	
Vincristine	12	6	0	0	yes	no	no
Vindesine	2	0	0	0		-	
Vismodegib	1	0	0	1		no	
Vitamin B12	6	4	4	0		no	
Vitamin D	14	10	2	0		no	
Vitamin E	3	2	0	0		no	
Warfarin	9	0	3	0	yes	no	no
Zidovudine	0	5	0	1		no	
Ziprasidone	2	0	0	2		yes	
Zolpidem	15	23	4	1		yes	no
Zonisamide	4	1	1	1		yes	
Zopiclone	3	7	1	0		no	
Zuclopenthixol	9	0	0	2		-	yes

Table 37. List with Interesting Drugs that might Interact with Nabiximols. *Column 1: Drugs; Column 2: Number of reports from people over or equal 50 years old that contain this drug; Column 3: Number of reports from people under 50 years old that contain this drug; Column 4: Number of reports from people with no defined age that contain this drug; Column 5: Prediction of correlation in between pharmacokinetic and pharmacodynamic interaction from 'PK-PD-Correlation' Table; Column 6: Known interactions from literature (no guarantee of completeness); Column 7: Interaction regarding 'Wechselwirkungscheck' on DocCheck and 'drug interactions checker' on drug.com (see 2.2.2.3 drug interactions); Column 8: Note, if drug might be interesting for further analysis or future studies; Colors: light red - over 1% frequency, dark red - over 10% frequency; Additional information e.g data sources, details about interaction etc. is available in Excel file '*List with Interesting Drugs'

Drugs	# of reports ≥ 50 years	# of reports < 50 years	# of reports not defined age	Drug Interaction Prediction (# of correlation)	Known Interactions (Literature)	Interactions Checker	INTERESTING DRUGS
Abatacept	0	0	0	0		no	
Acetaminophen	2	1	1	0		no	yes
Acetylcysteine	0	0	0	0		no	
Acyclovir	0	0	0	0		no	
Adalimumab	0	0	0	0		no	
Alendronic Acid	0	0	0	0		no	
Alfuzosin	0	0	0	0		no	
Alimemazine	0	0	0	0		-	
Alizapride	0	0	0	0		no	
Allopurinol	0	0	0	0		no	
Alprazolam	1	1	0	2		yes	
Amantadine	0	0	0	0		no	
Aminosalicylic Acid	0	0	0	0		no	
Amiodarone	1	0	0	0		no	
Amisulpride	0	0	0	0		no	
Amitriptyline	0	0	0	2		yes	
Amlodipine	2	0	0	0		yes	no
Amoxapine	0	0	0	1		yes	
Amoxicillin	0	0	0	0		no	
Amphetamine	0	0	0	2		no	
Ampicillin	0	0	0	0		no	
Anakinra	0	0	0	0		no	
Apixaban	0	0	0	0		no	
Apremilast	0	0	0	0		no	
Aprepitant	0	0	0	0		no	
Aripiprazole	0	0	0	0		yes	
Armodafinil	0	0	0	0		no	
Arnica Montana Flower	0	0	0	0		no	
Ascorbic Acid	0	0	0	0		no	
Aspirin	1	0	0	0		no	
Atenolol	0	0	0	2		yes	
Atorvastatin	0	0	0	0		no	
Atropine	0	0	0	0		no	
Avelumab	0	0	0	0		no	
Azithromycin	0	0	0	0		no	
Baclofen	9	3	5	0		yes	yes

Beclomethasone Dipropionate	0	0	0	0		no	
Benazepril	0	0	0	0		yes	
Benperidol	0	0	0	0		-	
Benzatropine	0	0	0	0		-	
Benzodiazepine	0	0	0	0		-	
Benzoylecgonine	0	0	0	0		-	
Bevacizumab	0	0	0	0		no	
Bictegravir	0	0	0	0		no	
Biotin	0	0	0	0		no	
Bisacodyl	0	0	0	0		no	
Bisoprolol	0	0	0	0		yes	
Bleomycin	0	0	0	0		no	
Boceprevir	0	0	0	2		no	
Bosentan	0	0	0	0		no	
Brimonidine	0	0	0	0		yes	
Brinzolamide	0	0	0	0		no	
Brivanib Alaninate	0	0	0	0		-	
Brivaracetam	0	0	0	2		yes	
Bromazepam	0	0	0	0		-	
Budesonide	0	0	0	0		no	
Bumetanide	0	0	0	0		yes	
Bupivacaine	0	0	0	0		no	
Buprenorphine	0	0	0	0		yes	
Bupropion	0	0	0	2		no	
Buspirone	0	0	0	0		yes	
Butalbital	0	0	0	0		yes	
Caffeine	0	0	0	0		no	
Calcium	0	0	0	0		no	
Calcium Carbonate	0	0	0	0		no	
Calcium Chloride	0	0	0	0		no	
Calcium Phosphate	0	0	0	0		no	
Canakinumab	0	0	0	0		no	
Candesartan	1	0	1	1		yes	
Carbamazepine	0	0	0	1		yes	
Carbazochrome	1	0	0	0		-	
Carbidopa	0	0	0	0		no	
Carboplatin	0	0	0	0		no	
Carboxymethylcellulose	0	0	0	0		no	
Cariprazine	0	0	0	1		yes	
Carisoprodol	0	0	0	1		yes	
Carvedilol	0	0	0	1		yes	
Cefaclor	0	0	0	0		no	
Cefepime	0	0	0	0		no	
Ceftriaxone	0	0	0	0		no	
Cefuroxime	0	0	0	0		no	
Celecoxib	0	0	0	0		no	
Cephalexin	0	0	0	0		no	

Cetirizine	0	0	0	0		yes	
Cetuximab	0	0	0	0		no	
Chlordiazepoxide	0	0	0	0		yes	
Chlorpromazine	0	0	0	1		yes	
Chlorthalidone	0	0	0	0		yes	
Cholecalciferol	0	0	0	0		no	
Cholestyramine	0	0	0	0		no	
Chondroitin Sulfate	0	0	0	0		no	
Cilostazol	0	0	0	0		no	
Ciprofloxacin	0	0	0	0		no	
Cisplatin	0	0	0	0		no	
Citalopram	0	0	0	0		yes	
Citicoline	0	0	0	0		no	
Citric Acid	0	0	0	0		no	
Clavulanic Acid	0	0	0	0		no	
Clindamycin	0	0	0	0		no	
Clobetasol	0	0	0	0		no	
Clobetasol Propionate	0	0	0	0		no	
Clonazepam	0	0	1	1		yes	
Clonidine	0	0	0	3		yes	
Clopidogrel	1	0	0	0		no	
Clotrimazole	0	0	0	0		no	
Clozapine	0	0	0	3		yes	
Cobalamin	0	0	0	0		no	
Cobimetinib	0	0	0	1		no	
Cocaine	0	0	0	1		no	
Codeine	1	0	0	1		yes	
Colchicine	0	0	0	0		no	
Colestipol	0	0	0	0		no	
Collagen	0	0	0	0		no	
Conjugated Estrogens	0	0	0	0		no	
Corticotropin	0	0	0	2		no	
Cortisone Acetate	1	0	0	0		no	
Crizotinib	0	0	0	2		no	
Curcumin	0	0	0	0		-	
Cyclizine	0	0	0	0		yes	
Cyclobenzaprine	0	0	0	0		yes	
Cyclophosphamide	0	0	0	0		no	
Cyclosporine	0	0	0	2		no	
Dabigatran Etexilate	0	0	0	0		no	
Daclatasvir	0	0	0	0		no	
Dalfampridine	2	1	1	0		no	yes
Dantrolene	0	0	0	0		yes	
Danvatirsen	0	0	0	0		-	
Daprodustat	0	0	0	0		-	
Darbepoetin Alfa	0	0	0	0		no	
Darunavir	0	0	0	0		no	

Dasabuvir	0	0	0	0		no	
Dasatinib	0	0	0	1		no	
Deflazacort	0	0	0	0		no	
Denosumab	0	0	0	0		no	
Desloratadine	0	0	0	0		no	
Desmopressin	0	0	0	0		no	
Desvenlafaxine	0	0	0	1		yes	
Dexamethasone	1	0	1	0		no	
Dextroamphetamine	0	0	0	0		no	
Dextromethorphan	0	0	0	0		yes	
Dextropropoxyphene	0	0	0	0		-	
Diamorphine	0	0	0	0		-	
Diazepam	0	0	1	1		yes	
Diclofenac	0	0	0	0		no	
Dicyclomine	0	0	0	0		no	
Digoxin	0	0	0	0		no	
Dihydrocodeine	0	0	0	2		yes	
Diltiazem	0	0	0	0		yes	
Dimenhydrinate	0	0	0	0		yes	
Diosmin	0	0	0	0		-	
Diphenhydramine	0	0	0	0		yes	
Diphenoxylate	0	0	0	0		yes	
Docusate	1	0	0	0		no	
Dofetilide	0	0	0	1		no	
Domperidone	0	0	0	0		-	
Donepezil	0	0	0	0		no	
Dopamine	0	0	0	0		no	
Dorzolamide	0	0	0	0		no	
Doxazosin	1	0	1	1		yes	
Doxepin	0	0	0	0		yes	
Doxorubicin	0	0	0	1		no	
Doxycycline	0	0	0	0		no	
Droperidol	0	0	0	0		yes	
Duloxetine	0	0	0	1		yes	
Durvalumab	0	0	0	0		no	
Dutasteride	0	0	0	0		no	
Efavirenz	0	0	0	1		no	
Emtricitabine	0	0	0	0		no	
Enalapril	0	0	0	0		yes	
Enoxaparin	0	0	0	0		no	
Entacapone	0	0	0	0		yes	
Enzalutamide	0	0	0	2		no	
Ephedrine	0	0	0	0		no	
Epinephrine	0	0	0	0		no	
Epirubicin	0	0	0	0		no	
Eplerenone	1	0	0	0		yes	
Erenumab	0	0	0	0		no	

Ergocalciferol	0	1	0	0		no	
Erlotinib	0	0	0	0		no	
Erythromycin	1	0	0	0		no	
Erythropoietin	0	0	0	0		-	
Escitalopram	0	4	0	0		yes	no
Eslicarbazepine	0	0	0	1		yes	
Esomeprazole	1	1	0	0		no	
Estradiol	0	0	0	0		no	
Eszopiclone	0	0	0	0		yes	
Etanercept	0	0	0	0		no	
Ethambutol	0	0	0	0		no	
Ethanol	0	0	0	0		yes	
Etoposide	0	0	0	0		no	
Everolimus	0	0	0	2		no	
Evolocumab	0	0	0	0		no	
Ezetimibe	0	0	0	0		no	
Famciclovir	0	0	0	0		no	
Famotidine	0	0	0	0		no	
Febuxostat	0	0	0	0		no	
Felodipine	0	0	0	0		yes	
Fenfluramine	0	0	0	0		no	
Fenofibrate	0	0	0	0		no	
Fentanyl	1	0	0	2		yes	
Ferrous Gluconate	0	0	0	0		no	
Ferrous Sulfate Anhydrous	0	0	0	0		no	
Fexofenadine	0	0	0	0		no	
Finasteride	0	0	0	0		no	
Fingolimod	1	5	1	0		no	no
Fish Oil	0	0	0	0		no	
Fluconazole	0	0	0	0		no	
Fludarabine	0	0	0	0		no	
Fludrocortisone	0	0	0	0		no	
Flunitrazepam	0	0	0	0		-	
Fluorouracil	0	0	0	0		no	
Fluoxetine	0	0	0	1		yes	
Flupentixol	0	0	0	0		-	
Flurazepam	0	0	0	0		yes	
Fluticasone	0	0	0	0		no	
Fluticasone Propionate	0	0	0	0		no	
Folic Acid	0	0	0	0		no	
Formoterol	0	0	0	0		no	
Fosamprenavir	0	0	0	0		no	
Fosaprepitant	0	0	0	0		no	
Fosinopril	0	0	0	0		yes	
Furosemide	0	1	0	0		yes	
Gabapentin	1	1	1	0		yes	
Gabapentin Enacarbil	0	0	0	0		yes	

Garlic	0	0	0	0		no	
Gemcitabine	0	0	1	0		no	
Gemfibrozil	0	0	0	0		no	
Glatiramer	1	0	0	0		no	
Glecaprevir	0	0	0	0		no	
Glimepiride	0	0	0	0		no	
Glipizide	0	0	0	0		no	
Glucosamine	0	0	0	0		no	
Glyburide	0	0	0	0		no	
Gold	0	0	0	0		-	
Granisetron	0	0	1	0		no	
Guaifenesin	0	0	0	0		no	
Haloperidol	0	0	0	2		yes	
Heparin	0	0	0	0		no	
Hesperidin	0	0	0	0		-	
Human Interferon Beta	2	0	0	0		-	yes
Hyaluronic Acid	0	0	0	0		-	
Hydralazine	0	0	0	0		yes	
Hydrochlorothiazide	0	0	0	0		yes	
Hydrocodone	0	0	1	0		yes	
Hydrocortisone	0	0	0	0		no	
Hydromorphone	0	1	0	1		yes	
Hydroxychloroquine	0	0	0	0		no	
Hydroxyzine	0	0	0	0		yes	
Hyoscyamine	0	0	0	0		no	
Ibandronate	0	0	0	0		no	
Ibuprofen	0	0	0	0		no	
Imatinib	0	0	0	1		no	
Imidazole Salicylate	0	0	0	0		-	
Indapamide	0	0	0	0		yes	
Infliximab	0	0	0	0		no	
Influenza Virus Vaccine	0	0	0	0		no	
Insulin Aspart	0	0	0	0		no	
Insulin Detemir	0	0	0	0		no	
Insulin Glargine	1	0	0	0		no	
Insulin Human	0	0	0	0		no	
Insulin Lispro	0	0	0	0		no	
Interferon alfa-n1	0	0	0	0		no	
Interferon beta-1a	0	0	0	0		no	
Interferon beta-1b	0	0	0	0		no	
Ipilimumab	0	0	0	0		no	
Ipratropium	0	0	0	0		no	
Irbesartan	0	0	0	0		yes	
Iron	0	0	0	0		no	
Isosorbide Dinitrate	1	0	0	0		yes	
Isosorbide Mononitrate	0	0	0	0		yes	
Isotretinoin	0	0	0	0		no	

Keratin	0	0	0	0		-	
Ketoconazole	0	0	0	0	yes	no	
Krill Oil	0	0	0	0		no	
Labetalol	0	0	0	0		yes	
Lacosamide	0	0	0	0		no	
Lactic Acid	0	0	0	0		no	
Lactobacillus Acidophilus	0	0	0	0		no	
Lactulose	0	1	0	0		no	
Lamivudine	0	0	0	0		no	
Lamotrigine	0	0	0	0		yes	
Lanreotide	0	0	0	1		no	
Lansoprazole	0	0	0	0		no	
Lapatinib	0	0	0	1		yes	
Latanoprost	0	0	0	0		no	
Lavender Oil	0	0	0	0		no	
Ledipasvir	0	0	0	0		no	
Leflunomide	0	0	0	0		no	
Lenalidomide	0	0	0	0		no	
Lenvatinib	0	0	0	2		no	
Letrozole	0	0	0	0		no	
Leucovorin	0	0	0	0		no	
Levetiracetam	0	0	1	0		yes	
Levodopa	0	0	1	0		no	
Levofloxacin	0	0	0	0		no	
Levomefolic Acid	0	0	0	0		no	
Levosalbutamol	0	0	0	0		-	
Levothyroxine	0	0	0	0		no	
Lidocaine	0	0	0	0		no	
Linagliptin	0	0	0	0		no	
Linezolid	0	0	0	0		no	
Liothyronine	0	0	0	0		no	
Liotrix	0	0	0	0		no	
Lisinopril	0	0	0	0		yes	
Lithium Aspartate	0	0	0	0		-	
Lithium Carbonate	0	0	0	0		yes	
Loperamide	0	0	0	0		no	
Loratadine	0	0	0	0		no	
Lorazepam	0	0	0	2		yes	
Losartan	0	0	0	0		yes	
Lovastatin	0	0	0	0		no	
Loxapine	0	0	0	0		yes	
Lubiprostone	0	0	0	0		no	
Lurasidone	0	0	0	1		yes	
Lysergic Acid Diethylamide	0	0	0	0		-	
Magnesium	0	1	0	0		no	
Magnesium Aspartate	0	0	0	0		no	

Magnesium Chloride	0	0	0	0		no	
Magnesium Hydroxide	0	0	0	0		no	
Magnesium Oxide	0	0	0	0		no	
Meclizine	0	0	0	1		yes	
Megestrol Acetate	0	0	0	0		no	
Melatonin	0	0	0	0		no	
Meloxicam	0	0	0	0		no	
Memantine	0	0	0	0		no	
Menthol	0	0	0	0		no	
Meperidine	0	0	0	0		yes	
Meprobamate	0	0	0	0		yes	
Mesalazine	0	0	0	0		-	
Metamizole	1	0	0	0		-	
Metformin	1	0	0	0		no	
Methadone	0	0	0	0		yes	
Methamphetamine	0	0	0	0		no	
Methocarbamol	0	0	0	0		yes	
Methotrexate	0	0	0	0		no	
Methotrimeprazine	0	0	0	0		yes	
Methsuximide	0	0	0	0		yes	
Methylpyrrolidone	0	0	0	0		-	
Methylcellulose	0	0	0	0		no	
Methylcobalamin	0	0	0	0		no	
Methylphenidate	0	0	0	0		no	
Methylprednisolone	5	2	3	0		no	yes
Methyltestosterone	0	0	0	0		no	
Metoclopramide	0	0	0	1		yes	
Metolazone	0	0	0	0		yes	
Metoprolol	1	0	0	0		yes	
Metronidazole	0	0	0	0		no	
Midodrine	0	0	0	0		no	
Midomafetamine	0	0	0	0		-	
Minocycline	0	0	0	0		no	
Mirtazapine	0	0	1	1		yes	
Modafinil	0	0	0	0		no	
Mometasone	0	0	0	0		no	
Mometasone Furoate	0	0	0	0		no	
Montelukast	0	0	0	0		no	
Morphine	0	0	1	0		yes	
Moxifloxacin	0	0	0	0		no	
Mycophenolic Acid	0	1	0	0		no	
Nabumetone	0	0	0	0		no	
Naldemedine	0	0	0	0		no	
Naloxone	0	0	0	0		no	
Naltrexone	0	0	0	0		no	
Naphazoline	0	0	0	0		no	
Naproxen	0	0	0	0		no	

Nebivolol	1	0	0	0		yes	
Nevirapine	0	0	0	0		no	
Niacin	0	0	0	0		no	
Niacinamide	0	0	0	0		no	
Nicardipine	0	0	0	0		yes	
Nicotine	0	0	0	0		no	
Nifedipine	0	0	0	0		yes	
Nitrofurantoin	0	0	0	0		no	
Nitroglycerin	0	0	0	0		yes	
Nivolumab	0	0	0	0		no	
Nordazepam	0	0	0	0		-	
Norepinephrine	0	0	0	0		no	
Nortriptyline	0	0	0	0		yes	
Nystatin	0	1	0	0		no	
Ocrelizumab	2	1	1	0		no	yes
Octreotide	0	0	0	2		no	
Olanzapine	0	1	0	2		yes	
Olopatadine	0	0	0	0		yes	
Ombitasvir	0	0	0	0		no	
Omega-3 Fatty Acids	0	1	0	0		no	
Omega-6 Fatty Acids	0	0	0	0		-	
Omeprazole	0	0	0	0	no	no	
Ondansetron	0	0	0	0		no	
Opipramol	0	0	0	0		-	
Orphenadrine	0	0	0	0		yes	
Osimertinib	0	0	0	0		no	
Oxaliplatin	0	0	0	0		no	
Oxazepam	0	0	0	0		yes	
Oxcarbazepine	0	0	0	2		yes	
Oxybutynin	1	0	0	2		no	
Oxycodone	1	1	1	1		yes	
Oxymorphone	0	0	0	2		yes	
Oxyquinoline	0	0	0	0		-	
Paclitaxel	0	0	1	1		no	
Palbociclib	0	0	0	0		no	
Paliperidone	0	0	0	0		yes	
Palonosetron	0	0	0	0		no	
Pancrelipase Amylase	0	0	0	0		no	
Pancrelipase Lipase	0	0	0	0		no	
Pancrelipase Protease	0	0	0	0		no	
Pantoprazole	2	0	0	0		no	yes
Pantothenic Acid	0	0	0	0		-	
Paritaprevir	0	0	0	2		no	
Paroxetine	0	0	0	1		yes	
Peginterferon alfa-2a	0	0	0	0		no	
Peginterferon alfa-2b	0	0	0	2		no	
Pembrolizumab	0	0	0	0		no	

Pemetrexed	0	0	0	0		no	
Pentamidine	0	0	0	1		no	
Pentazocine	0	0	0	0		yes	
Perampanel	0	0	0	1		yes	
Perindopril	0	0	0	0		yes	
Phencyclidine	0	0	0	0		no	
Pheniramine	0	0	0	0		no	
Phenobarbital	0	0	0	0		yes	
Phenoxymethylpenicillin	0	0	0	0		-	
Phentermine	0	0	0	0		no	
Phenylbutazone	0	0	0	0		no	
Phenytoin	0	0	0	0		yes	
Pibrentasvir	0	0	0	0		no	
Pipamperone	0	0	0	0		-	
Piracetam	0	0	1	0		-	
Pirfenidone	0	0	0	1		no	
Piritramide	0	0	0	0		-	
Piroxicam	0	0	0	0		no	
Polyethylene Glycol	0	0	0	0		no	
Posaconazole	0	0	0	2		no	
Potassium	0	0	0	0		-	
Potassium Chloride	0	0	0	0		no	
Pramipexole	0	0	0	0		yes	
Prasterone	0	0	0	0		no	
Prasugrel	0	0	0	0		no	
Pravastatin	0	0	0	0		no	
Prazosin	0	0	0	0		yes	
Prednisolone	0	0	0	0		no	
Prednisone	0	4	0	0		no	no
Pregabalin	2	0	1	0		yes	no
Primidone	0	0	1	0		yes	
Procarbazine	0	0	0	0		no	
Prochlorperazine	0	0	0	0		yes	
Procyclidine	0	0	0	0		yes	
Progesterone	0	0	0	1		no	
Promethazine	0	0	0	0		yes	
Propafenone	0	0	0	0		no	
Propiverine	0	0	0	0		-	
Propranolol	0	0	1	0		yes	
Propyphenazone	0	0	0	0		-	
Prothipendyl	0	0	0	0		-	
Prucalopride	0	0	0	0		no	
Pseudoephedrine	0	0	0	0		no	
Psyllium (Plantago Seed)	0	0	0	0		no	
Pyridoxine	0	0	0	0		no	
Pyrimethamine	0	0	0	0		no	
Quetiapine	0	1	0	2		yes	

Quinapril	0	0	0	0		yes	
Quinidine	0	0	0	0		no	
Quinine	0	0	0	1		no	
Rabeprazole	0	0	0	0		no	
Raloxifene	0	0	0	0		no	
Ramipril	1	0	0	0		yes	
Ranitidine	0	0	0	0		no	
Repaglinide	0	0	0	0		no	
Ribavirin	0	0	0	0		no	
Riboflavin	0	0	0	0		no	
Rifampicin	0	0	0	0	yes	no	
Rimantadine	0	0	0	0		no	
Riociguat	0	0	0	1		no	
Risedronic Acid	0	0	0	0		no	
Risperidone	0	1	0	2		yes	
Ritonavir	0	0	0	2		no	
Rituximab	0	0	0	0		no	
Rivaroxaban	0	0	0	0		no	
Rivastigmine	0	0	0	0		no	
Rofecoxib	0	0	0	0		no	
Ropinirole	0	0	0	2		yes	
Rosiglitazone	0	0	0	0		no	
Rosuvastatin	0	0	0	0		no	
Rucaparib	0	0	0	2		no	
Salbutamol	0	0	0	1		no	
Salicylic Acid	0	0	0	0		no	
Salmeterol	0	0	0	0		no	
Sargramostim	0	0	0	0		no	
Scopolamine	0	0	0	0		no	
Selegiline	0	0	0	1		no	
Sennosides	1	0	0	0		no	
Serine	0	0	0	0		-	
Serrapeptase	0	0	0	0		-	
Sertraline	0	0	0	1		yes	
Sevelamer	0	0	0	0		no	
Sildenafil	0	0	0	0		no	
Silodosin	0	0	0	0		yes	
Simvastatin	1	0	0	0		no	
Sipuleucel-T	0	0	0	0		no	
Sitagliptin	0	0	0	0		no	
Sodium Aurothiomalate	0	0	0	0		no	
Sodium Bicarbonate	0	0	0	0		no	
Sodium Chloride	0	0	0	0		no	
Sodium Citrate	0	0	0	0		no	
Sodium Lauryl Sulfoacetate	0	0	0	0		-	
Sodium Oxybate	0	0	0	0		no	
Sofosbuvir	0	0	0	0		no	

Sorafenib	0	0	0	2		no	
Sorbitol	0	0	0	0		no	
Sotalol	0	0	0	2		yes	
Spironolactone	0	0	0	0		yes	
Stavudine	0	0	0	0		no	
Sucralfate	0	0	0	0		no	
Sulbactam	0	0	0	0		no	
Sulfamethoxazole	0	0	0	0		no	
Sulfasalazine	0	0	0	0		no	
Sulpiride	0	0	0	0		-	
Sumatriptan	0	0	0	0		no	
Sunitinib	0	0	0	2		no	
Tacrolimus	0	1	0	2		yes	
Tadalafil	0	1	0	0		no	
Tamsulosin	1	0	0	0		yes	
Tapentadol	0	0	0	1		yes	
Tegaserod	0	0	0	0		no	
Telaprevir	0	0	0	1		no	
Telmisartan	0	0	0	0		yes	
Temazepam	0	0	0	0		yes	
Tenofovir	0	0	0	0		no	
Terazosin	0	0	0	0		yes	
Terbinafine	0	0	0	0		no	
Teriflunomide	1	0	0	0		no	
Teriparatide	0	0	0	0		no	
Testosterone	0	0	0	0		no	
Testosterone Undecanoate	0	0	0	0		no	
Theophylline	0	0	0	0	yes	yes	
Thiamine	0	0	0	0		no	
Timolol	0	0	0	0		yes	
Tiotropium	0	0	0	0		no	
Tizanidine	0	0	0	2		yes	
Tobacco Leaf	0	0	0	0		-	
Tocilizumab	0	0	0	0		no	
Tofacitinib	0	0	0	0		no	
Tolterodine	0	0	0	0		no	
Topiramate	0	0	1	1		yes	
Topotecan	0	0	0	0		no	
Torasemide	0	0	0	0		yes	
Tramadol	0	1	0	1		yes	
Trazodone	0	0	0	2		yes	
Triamcinolone	0	0	0	0		no	
Triamterene	0	0	0	0		yes	
Triazolam	0	0	0	1		yes	
Trimebutine	0	0	0	0		-	
Trimethoprim	0	0	0	0		no	
Trospium	0	0	0	0		no	

Turmeric	0	0	0	0		no	
Ubidecarenone	0	0	0	0		-	
Urelumab	0	0	0	0		-	
Ustekinumab	0	0	0	0		no	
Valproic Acid	0	0	0	1		yes	
Valsartan	0	0	0	0		yes	
Vancomycin	0	0	0	0		no	
Varenicline	0	0	0	0		no	
Vedolizumab	0	0	0	0		no	
Velpatasvir	0	0	0	1		no	
Vemurafenib	0	0	0	2		no	
Venetoclax	0	0	0	2		no	
Venlafaxine	0	0	0	1		yes	
Verapamil	0	0	0	0		yes	
Vilanterol	0	0	0	0		no	
Vincristine	0	0	0	0		no	
Vindesine	0	0	0	0		-	
Vismodegib	0	0	0	1		no	
Vitamin B12	0	0	0	0		no	
Vitamin D	0	0	0	0		no	
Vitamin E	0	0	0	0		no	
Warfarin	0	0	0	0		yes	
Zidovudine	0	0	0	0		no	
Ziprasidone	0	0	0	1		yes	
Zolpidem	0	0	0	0		yes	
Zonisamide	0	0	0	1		yes	
Zopiclone	0	0	0	0		no	
Zuclopenthixol	0	0	0	1		-	