PhD Dissertation of Sun Young Yum, MD

Signal Detection of Patient Subjective Drug Adverse Experiences Using the U.S. FDA Adverse Event Reporting System

Pharmacoepidemiologic Exploration of Increased Eating Drives Associated with Antidiabetic Medications

미 식약처 약물 감시 시스템 데이터베이스를 활용한
주관적 약물 부작용 경험에 대한 실마리 정보 탐색
약물역학연구: 당뇨 약제와 식욕 증가

August 2021

Graduate School of Medicine
Seoul National University
Clinical Medical Sciences

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Submitting a PhD Dissertation of
Medicine

April 2021

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July 2021

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ABSTRACT

During clinical development, much of the safety detection and analysis effort is centered on assessing the human equivalent of significant findings from animal toxicology studies. Moreover, toxicities hypothesized from primary and secondary pharmacologic effects profiling are also used for safety analysis. After a drug launches in the market, postmarketing safety surveillance systems focus mainly on hard outcomes of mortality, serious morbidity, or objectively quantifiable outcomes (e.g., laboratory data, imaging biomarkers). Institutions using these pillars of drug safety have not had much interest in examining “soft signs” or subjective patient drug experiences.

This study explores whether an existing pharmacovigilance database, namely the U.S. Food and Drug Administration’s Adverse Events Reporting System (FAERS), can be used to examine soft signals of subjective patient experiences, especially those related to motivational aspects of eating.

Antidiabetic drugs were used to examine whether subjective patient drug experiences of increased eating drives could be detected using the FAERS. Referencing U.S. prescription data, 15 non-insulin, single agent antidiabetic drugs (ADDs) most frequently prescribed in the United States from 6 ADD classes were used. Event terms used to extract adverse drug reactions (ADRs)

of increased eating drives were *hunger*, *food craving*, and *increased appetite*. An aggregate search was also performed combining the 3 event terms. Drug-event pairs were extracted for periods of FAERS existence from 1968 to December 31, 2020. The reporting odds ratio (ROR) was used for a disproportionality calculation in which a ROR with a lower margin of the 95% CI >1 was defined as a positive ADR signal.

All ADD classes yielded positive safety signals of increased eating drives: ROR [95% CI] calculations ranging from 2.00 [1.74, 2.31] to 12.38 [11.81, 12.98]. For the individual ADDs, the RORs [95% CI] for increased eating drives were:

2.00 [1.74, 2.31] for metformin, 2.29 [1.46, 3.59] for linagliptin, 1.85 [0.96, 3.55] for saxagliptin, 3.20 [2.64, 3.89] for sitagliptin, 4.69 [4.06, 5.42] for dulaglutide, 16.22 [15.31, 17.18] for exenatide, 12.55 [11.42, 13.78] for liraglutide, 9.63 [7.50, 12.37] for semaglutide, 2.98 [2.39, 3.73] for canagliflozin, 6.93 [5.17, 9.29] for dapagliflozin, 2.49 [1.84, 3.37] for empagliflozin, 3.07 [2.12, 4.45] for glimepiride, 5.03 [3.90, 6.48] for glipizide, 3.31 [2.39, 4.57] for glyburide, and 3.06 [2.42, 3.87] for pioglitazone.

The FAERS contained substantial numbers of subjective patient experience ADRs. Out of over 20,000 event terms, the three event terms for increased eating drives totaled 0.1% of all case reports in the FAERS. Soft signals seem

to be more frequently reported by consumers than by healthcare providers. 69.33% of the reports of increased eating drives for all drugs were from consumers and 23.94% from healthcare providers. For all ADD classes, more reports of increased eating drives were received from consumers (33.82-89.70%) than healthcare providers (9.89-35.48%) and from women (57.26-72.45%) than men (25.64-34.36%).

Patients may offer information about previously unknown ADRs that physicians cannot observe or quantify. Educated consumers can be valuable partner in the post-marketing surveillance of drug safety. Patient distressful drug experiences can affect treatment adherence and therapeutic. FAERS and other patient reporting systems might be useful tools in detecting adverse patient drug experiences.

Keywords: hunger, appetite, soft safety signals, subjective drug experience, anti-diabetic, postmarketing pharmacovigilance, signal detection, FAERS

Student number: 2014-30913

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1. INTRODUCTION

1.1. Pharmacovigilance systems

The concept of drug safety, which initially focused on activities to minimize risk, evolved to pharmacovigilance (PV) systems that emphasize continued watchful monitoring of drug safety before marketing as well as after-market authorization. Formal PV systems evolved differently across the globe, and despite attempts at harmonization, legislation governing the regulation of medicines differs considerably around the world. In the United States, PV activities are governed by the Code of Federal Regulations Title 21 (U.S. Food and Drug Administration [FDA], 2020a). The EU PV system is defined in the Good Pharmacovigilance Practices (GVP), which includes 16 guidance documents (Module I–XVI) released by the European Medicines Agency (EMA, 2021). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for PV are outlined in E2A–E2F documents (ICH, n.d.).

1.1.1. Rationale for legislation: protection of public health

The objectives of regulatory agencies in enacting PV legislation are to protect public health. Adverse drug reactions (ADR) contribute to a significant portion of all hospital admissions, are one of the most common causes of

hospital deaths, and account for increasing societal costs (Classen et al., 1997; Gyllensten et al., 2013; Leape et al., 1991). In the GVP, the objectives of PV and applicable legislation are to (1) prevent harm from adverse reactions and (2) promote the safe and effective use of medicinal products (EMA, 2017b).

1.1.2. Definitions

ICH E2A and E2D guidelines define an "adverse event" (AE) as any untoward event that occurs while taking a drug, which is not necessarily causally related. A "side effect" is an unintended effect, whether positive or negative. "Side effect" is now considered a dated term to be avoided. The key difference between an AE and an ADR is that an ADR implies a causal relationship. The ICH E2A specifies preapproval and post-approval ADR definitions based on established therapeutic doses. In the post-approval setting, an ADR occurs at doses normally used (ICH, n.d.). This thesis accepts the definitions of AEs and ADRs and considers both depending on the specific context. The E2A guideline was first finalized in 1994 and implemented in Europe the same year. The United States, Canada, and Japan adopted the E2A guideline in 1995, and Korea implemented the guideline in June 2018 by a Prime Minister's Decree.

1.1.3. Sources of report

Sources of safety data include clinical trials, literature reports, spontaneous reports, and solicited reports. The FDA requires spontaneous reports to be treated as reactions on the assumption that the reporting is motivated by a suspicion of causality. In contrast, EU and Japanese regulations leave open the possibility of "not related" spontaneous reports. Solicited reports include data collected in an organized manner, for instance, from patient support programs, disease management programs, and surveys.

1.1.4. Valid report

To ensure the right information is collected in a consistent and timely manner, reporting standards have been developed. Data collection standards include reporting timelines based on the seriousness of the event, harmonized terminology, and standards for what constitutes a valid individual case safety report (ICSR) that can be internationally exchanged. A valid ICSR includes an identifiable patient, drug, event, and an identifiable reporter (EMA, 2017a). The FDA's MedWatch forms have other fields that can be entered such as age, date of birth, gender, weight, ethnicity, race, the outcome of the event (death, life-threatening, hospitalization, disability, congenital anomaly, other serious or important effects, required intervention to prevent permanent impairment), date of the event, relevant laboratory data, other relevant histories, drug information (strength, manufacturer, lot#, dose), treatment dates, diagnosis for use, de-challenge (drug is withdrawn), re-challenge (drug is re-administered)

outcome, concomitant medications, reporter details (address, phone, email, occupation) (FDA, 2020b). However, only drug, event, and the reporter's name are required for a report to be processed.

1.1.5. Coding of AEs: MedDRA

The Medical Dictionary for Regulatory Activities (MedDRA) was developed by the ICH to achieve internationally exchangeable consistency in adverse event terminology. The MedDRA is the established common standard used for classifying and coding AE for both clinical trials and postmarketing reports. The dictionary is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) as a trustee of the ICH. The Maintenance and Support Services Organization (MSSO) maintains, updates and distributes MedDRA. Proposed changes submitted by MedDRA users are reviewed by MSSO staff, who include physicians and support personnel (MedDRA, 2021a).

The five-level hierarchical structure of MedDRA is graphically presented in Figure 1. At the bottom of the hierarchy are the lower-level terms (LLTs), which is close to how AEs are observed and reported. These LLTs are followed by preferred terms (PT), which are generally symptoms, signs, diagnoses, abnormal investigations (physical exam, laboratory values), and procedures. The PTs are grouped in higher-level terms (HLTs) based on

anatomy, physiology, and pathology, which are further grouped into high-level group terms (HLGTs) belonging at the top of the hierarchy of 26 system organ classes (SOCs).

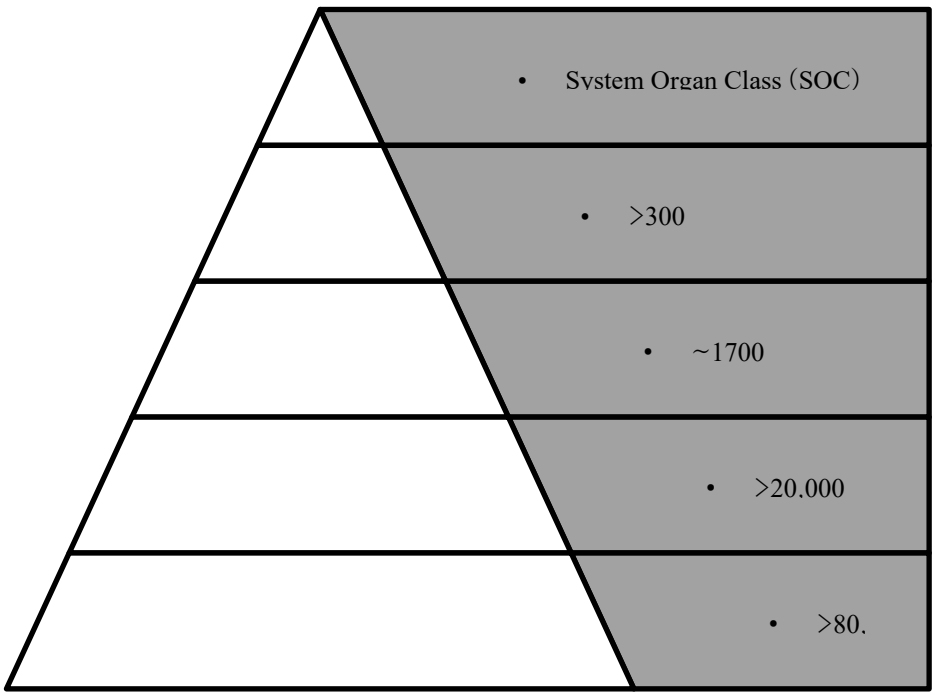

Figure 1. MedDRA hierarchy is structured into 5 levels from specific to general. The number of terms in each level is displayed as well as an example term at each level. The example terms are linked through the hierarchy.

The hierarchy is multiaxial, that is, one condition may affect multiple organ or pathologic processes. An example used in the MedDRA training information to illustrate this is the PT *influenza*, which falls under 2 SOCs: *infections and infestations* and *respiratory, thoracic, mediastinal disorders.* The hierarchy may not be intuitive in its intent or classification. For example, while

substance use is a PT, *tobacco use* is an HLT (MedDRA, 2021a).

During clinical trials, depending on company policies, most organizations will code AEs either at the level of a PT or an LLT (Winter, 2011). For regulatory reporting, AEs are tabulated into SOC-PTs. LLTs are collected to further understand the details of the signals detected at the PT level. For example, whereas a PT *otitis externa* is probably a sufficient level of information to guide signal detection, looking at the LLT *bilateral otitis externa* may help understand the nature of the PT. Another example is the PT *contusion*, which can be further specified into LLTs with the bruise location. Each LLT is linked to only one PT, whereas a PT may be linked to multiple LLTs.

When verbatim patient descriptions of an experience are reported, they are coded into a MedDRA term by a PV associate, who is most commonly a person with a nursing background. At other times, clinical investigators or healthcare providers (HCPs) will assess the patient complaint and report an impression that is MedDRA coded or (Hasford et al., 2021) even report an MedDRA term themselves.

Standardization has been instrumental in the cross-agency international exchange of information as well as in structured comparative analyses. Although the MSSO has considerably developed the system, there are still aspects of the MedDRA that could be improved.

1.1.5.1. Splitting, lumping, exaggeration, minimization, miscoding

Splitting the same AE among similar terms may lead to missed safety signals. For example, elevated blood pressure may be split among the following terms: *diastolic hypertension*, *endocrine hypertension*, *essential hypertension*, *hypertension*, *labile hypertension*, *prehypertension*, *secondary hypertension* (and many other specific causes related to hypertension, such as *renovascular*, *right ventricular*, *procedural*, *postoperative*, etc.), *supine hypertension*, *white coat hypertension*, *blood pressure abnormal*, *blood pressure ambulatory abnormal*, *blood pressure ambulatory increased*, *blood pressure diastolic increased*, *blood pressure fluctuation*, *blood pressure increased*, *blood pressure orthostatic abnormal*, *blood pressure orthostatic increased*, *blood pressure systolic abnormal*, *blood pressure systolic increased*, *labile blood pressure*, and others.

On the opposite end, lumping different terms into a PT may also lead to missed signals. For example, verbatim reports of *eyelid swelling, swollen gums*, *leg swelling, swollen lip and swollen tongue* can be specifically coded by location or alternatively, a coding associate may code all of these events as *edema*. Such lumping is uninformative. Eyelid swelling may be an allergic reaction, whereas leg swelling may be a sign of congestive heart failure.

Sometimes events are exaggerated through the coding process, for example, verbatim “dizziness” might be coded as *syncope*; or minimized, for instance, a

syncopal episode coded as *hypotension*. Lastly, the coding may be wrong. For instance, “better mood” might be coded as *euphoria*, or “colors seem brighter” as *visual impairment*, which can completely misdirect future risk management.

During the course of clinical development, a physician from the clinical study team or the clinical development team will review all AEs, particularly those that might lead to labeling implications. The case is further discussed with an investigator, who is asked to clarify issues with the patients to raise the likelihood of a more appropriate coding. In the postmarketing setting, there is no such quality check. Hence, large numbers are relied upon to dilute such errors.

The FDA guides that AEs reported under different terms but representing the same phenomenon should ordinarily be grouped together as a single ADR to avoid diluting or obscuring the true effect (FDA, 2006a). However, different PV associates will have different terms they tend to use for the same condition. Linguistic and cultural differences or possibly patterns of practice may result in preferential coding of the same event into different PTs. It is difficult to reduce inter-coder variability, especially when there are more than 20,000 PTs. When AEs of particular interest are present, then coder training or a consensus process may help provide some consistency in coding.

Sometimes health authorities will request lumping of PTs that may be

considered relevant to increase the sensitivity of detection. For example, only narrow search terms directly referring to suicide and self-injury may be taken at face value to meaning suicide potential. However, other PTs may be related to suicidal intent or behavior, identification of which could increase the sensitivity for detecting a drug's potential to be associated with greater suicide risk. Such PTs might be related to overdose, poisoning, and symptoms known to be associated with suicide such as depression or substance abuse.

The Standardized MedDRA Queries (SMQs) were developed to define the scope of narrow and broad searches for conditions of high regulatory interest, that is, conditions that have serious or lasting outcomes (MedDRA, 2021b). Another coding scheme is the World Health Organization (WHO) Adverse Reaction Terminology (WHO-ART), mainly used outside the ICH regions. The WHO-ART PTs have been mapped to the corresponding MedDRA terms enabling collective analysis (WHO, 2020). The Japanese had a Japanese adaptation the J-ART, which was used in conjunction with the Japanese Medical Information System (MEDIS), now replaced with MedDRA.

1.1.6. Causality

Multiple stakeholders are involved in the assessment of causality during drug development, in particular, patients, physicians, and companies. Occasionally, a centralized determination is made of which events are reactions. Other times,

intensive investigations are conducted of medical contexts including interviews with the patient or caregiver, physician to assess causality. For regulatory reporting, only two categories exist: likely related and not related. Often, clinical trial databases collect relationships on a spectrum, for example, definite, probable, possible, unlikely, remote, and not related (Agency for Healthcare Research and Quality, 2014).

Aside from immunologic reactions, the main mechanisms of ADRs that are commonly considered are an exaggerated therapeutic response, off-target, or secondary pharmacologic effects. An anti-diabetic drug causing hypoglycemia would be an example of an exaggerated therapeutic response. An anti-dopaminergic action at the mesocorticolimbic pathways of an antipsychotic would be an on-target effect. However, the same action on the nigrostriatal and tuberoinfundibular pathways resulting in a movement disorder or hyperprolactinemia would be considered an off-target effect.

Characterization of the secondary pharmacology begins with in vitro pharmacologic profiling, often referred to as the "safety pharmacology screen." A high promiscuity rate (i.e., a high percentage of targets with significant binding) has been a predictor of a low probability of success of a drug in early discovery as well as a predictor of drug withdrawal (Bowes et al., 2012). Contextualization of binding and functional assays is key in understanding the potential causation of each target–drug reaction pair. This contextualization

includes a thorough evaluation of the available literature, such as the Online Mendelian Inheritance in Man, knock-out data, the International Union of Basic and Clinical Pharmacology guide, and pharmacological reference compounds. No harmonized standard for performing this process exists. Therefore, the process is largely dependent on the ability of scientists and clinicians involved in the drug development team to integrate and interpret the information.

As the molecular biology of human thought, emotions, and behaviors are not straight forward, subjective patient experiences are less likely to be predicted by secondary pharmacology. If for example, a molecular on-target effect is to reduce appetite, and a paradoxical increase in appetite is experienced, the causality interpretation based on biologic plausibility may be difficult. Hypothetically, it could be related to (1) loss of efficacy due to tolerance (e.g. desensitization of activity on target), effect of neutralizing antibodies, (2) secondary pharmacology, e.g. compensatory effects of related pathways, (3) homeostatic regulation, or (4) unrelated to the target.

1.1.7. Non-clinical safety

Up to registration, well-defined standards lay out what and how non-clinical data should be collected. Non-clinical studies conducted with 2 species, rodent and non-rodent (and additional species for special tox), enable clinical

trials of the investigational drug in healthy volunteers and patients. These data are focused on major organ toxicity, carcinogenicity, teratogenicity, and mutagenesis (FDA, 2010). Non-clinical data are not always reflective of clinical safety profiles. Moreover, animals are unable to verbalize subjectively unwanted or unpleasant effects. Such subjective effects can only be observed during human trials.

The MedDRA is not used in animal toxicology, and what an "adverse" event means in animal toxicology studies is different and less straightforward compared to humans (Pandiri et al., 2017). These differences add further complexity to translating animal toxicology reports to human safety.

Targets associated with major liabilities are well defined. For example, the integration of genetic, pharmacologic, and clinical data has defined which targets should be screened to assess cardiovascular safety liabilities, including heart rate, blood pressure, contractility, and those associated with structural cardiotoxicity (Cross et al., 2015). Unlike such quantifiable markers, aside from rare examples such as pain face, animals are not able to provide information on subjective drug experiences.

1.1.8. Clinical trial safety data

Clinical trials are artificial settings. Just as non-clinical experiments adopt a

reductionistic approach to alter one variable at a time to study its implication in isolation, clinical trials also attempt, as much as practical, to study the effects of a drug in isolation in a relatively homogenous sample. Numerous exclusion criteria are built into the study to exclude the effects of comorbidities (often common comorbidities in the target patient population), as well as concomitant medications that may have pharmacokinetic or pharmacodynamic interactions. Additionally, frail patients who are prone to AEs, or demanding, complaint-prone patients, as well as those with less than desired compliance or patients whose baseline characteristics stand out (e.g., a very high body mass index) also tend to be excluded. In fact, patients at greater risk of ADRs are often excluded. Furthermore, some studies define AEs with qualifiers such as "clinically significant." Some subjective patient experiences such as pain are more likely to be considered "clinically significant," whereas patient disclosure of hunger may be more likely not attended to or not captured as an AE.

Clinical trials are designed with the specific purpose of providing data outlined in the clinical development plan (in line with the target product profile) and the evidence generation plan (in line with value proposition profile or market access goals). Regarding safety, the goal is to test and generate data that achieves predefined goals of aspirational product labeling language. These goals are focused on minimizing risks that may be defined in a black-box labeling, warnings, drug-drug interactions, and dosage

adjustments in the liver- or renal-impaired patients.

Drug development focuses on drug approval and reimbursement; therefore, the safety analyses are structured to address each section of the prescribing label (FDA, 2021b). Additionally, easily objectively quantifiable specific system or organ toxicity is tested per regulatory guidance (e.g., a thorough QT study). With an abundance of hard signals to focus on, patient experiences such as increased eating drives (hunger, appetite, food craving) are possibly far down or nonexistent on the list of priorities except for the development of appetite suppressants. A crucial question concerns drugs to treat diabetes—a disorder in which food intake plays an essential role in short-term glycemic control and probably long-term morbidity and mortality.

The FDA has specific guidance on the safety data requirements for antidiabetic therapies. It require at least 500 patients with stage 3/4 chronic kidney disease, at least 600 patients with established cardiovascular (CV) disease (e.g., previous myocardial infarction, documented coronary artery disease, previous stroke, peripheral vascular disease) and at least 600 patients older than 65 years of age. The guidance stresses rigor applied to the assessment of CV outcomes, such as the adjudication of events (FDA, 2020c). In alignment with the regulatory ambiance, drug development clinical trials in diabetes focus on characterizing mortality, cardiovascular and other serious morbidities. Feeling hungry, increased appetite, and food cravings are not

likely considered “clinically significant” when the emphasis is on identifying serious risks.

From patient perspectives, those with diabetes might participate in clinical trials despite the chance of being randomized to placebo because of the intensity and frequency of interactions with and attention by healthcare professionals (Lawton et al., 2003). Psychologically, the intensity and frequency of attention from physicians and other healthcare professionals may increase general satisfaction with treatment including the investigational medicine, and seemingly trivial reactions such as experiencing changes in hunger, appetite, or food cravings might not be recognized or levied sufficient significance to be mentioned.

Feeling well and in control of one’s diabetes has been shown to reduce the motivation to participate in clinical trials (Estcourt et al., 2016). If patients entering the trial were motivated by inadequate control of blood sugar, then their attention on the outcome may be focused on glycemic control. Often, in clinical trials of conditions that use a numerically visible primary marker of disease control, (e.g., glucose, blood pressure, cholesterol, FEV1, FVC), patients may become obsessed with these numbers. Therefore, a decreased level of priority is placed on subjective experiences of the drug, such as effects on hunger and appetite.

1.1.9. Continuous characterization of safety in the post-market authorization

At the time of drug approval, much remains unknown about the drug, particularly regarding benefits and risks in patients who did not meet the extensive subject eligibility criteria for registration trials. Safety issues that are not serious, not readily quantifiable, or of clinical priority might not be adequately characterized. Drugs are approved for marketing when the demonstrated benefit is deemed to outweigh the identified risks as well as the risks of the unknown. To continue to discover the unknowns, especially concerning safety, postmarketing safety systems were developed and continue to evolve. Indeed, most safety knowledge is gained only after the product obtains a license and is widely used in the market.

In the EU, post-authorization safety studies (PASS) are often a condition of the market authorization, which is legally binding. A PASS may be required at the time of first authorization and or any time post-authorization. A PASS may also be voluntarily performed by the market authorization holder (EMA, 2012).

In the United States, a postmarketing study may be required by the FDA, agreed mutually with a new drug approval applicant, or proposed by the applicant (FDA, 2006b). In Title IX of the FDA Amendment Act (FDAAA) of 2007, the FDA gained enhanced authority regarding the postmarket safety of

drugs, including the authority to require postmarket studies, mandate safety labeling changes, and require risk evaluation and mitigation strategies (FDA, 2018b).

Postmarketing real-world safety and effectiveness studies in diabetes have focused on target organ disease, using outcomes such as major acute coronary events (MACE) as a composite endpoint, MACE components (coronary revalorization, acute coronary syndrome, stroke), heart failure, end-stage renal disease, and renal failure (FDA, 2018a).

1.2. Spontaneous reporting systems

Postmarketing pharmacovigilance relies on spontaneous reporting systems (SRS) except in cases where specific safety tests were required as a condition of the marketing authorization or a specific risk management program was agreed upon with the health authorities. The main purpose of an SRS is the detection of previously unrecognized "signals," that is, hypothesis generation. This reporting is followed by formal pharmacoepidemiology methods that test the hypothesis. Sufficient exposure is required to detect a signal. "Rule of 3," also referred to as "regulatory rule of 3" is a simple binomial calculation that yields an estimate of (0,3/n) to detect a serious ADR with 95% confidence (Hanley & Lippman Hand, 1983). For example, in detecting potential cases of drug-induced liver injury, if the rate of drug-induced Hy's Law cases is

1/1,000, about 3,000 exposed subjects would be needed to have a 95 percent probability of observing at least one Hy's Law case (FDA, 2009). As non-serious events are reported at a lower rate, the patient exposure will have to be greater to detect non-serious ADR signals.

1.2.1. Limitations of spontaneous reports

1.2.1.1. Under-reporting

Limitations of spontaneous reports include inherent underreporting. According to Side Effects.de from Medikura Digital Health, a patient-centered web-based ADR reporting system, only 1% of all side effects are officially passed on to the drug authorities (Side Effects.de, 2019). In the United States, it was estimated in 1987 that only 1% of serious ADRs were estimated to be reported (Scott et al., 1987). A 2017 estimation concluded that reporting rates of serious ADRs in the FAERS range from 0.7% for diabetes to 47.3% for multiple sclerosis (Advera Health Analytics, 2017).

In addition, a bias is seen toward reporting serious or severe reactions. For example, although the reference is dated, it has been estimated that only 10% of serious ADRs and 2–4% of non-serious ADRs are reported in the UK (Rawlins, 1995).

1.2.1.2. Lifecycle effect

Another well-established reporting bias is the Weber effect, also called the

"lifecycle effect," which describes a surge of spontaneous reports after a drug launch (from 6 months to 2 years) that eventually tapers down to a steady-state (Weber, 1984). First described by Weber in 1984, the effect was replicated in an analysis published in 2004 of the FDA AERS for drugs approved between 1968–2000 (Hartnell & Wilson, 2004). Hoffman et al. (2014) examined reporting frequency patterns for FAERS reports for drugs approved between 2006 and 2010; Weber's effect was not reported in the study. The authors suggested that the overall increase in awareness and reporting volumes since Weber's 1984 study may be the reason (Hoffman et al., 2014).

An alternative explanation for the observations by Hoffman is the more complex market access environments that makes it difficult to identify the launch time. Launch time is variable depending on each company's strategy. For some products, a non-reimbursed launch may occur, especially if it is estimated that there will be sufficient market demand despite the out-of-pocket expense. For other products, the launch will occur after reimbursement; the reimbursement process is highly variable across the globe, in which there can be single or multiple payors (private, government—central, local) in a given country. Depending on the unmet medical need and the urgency of treatment or the degree of value to patients, reimbursement negotiations can be a short or a long process. On a general note, fully reimbursed launches in major markets occur on average about 2 years after market authorization.

Some drugs that were launched into a reimbursed major market and later approved in the United States may have reporting peaks immediately after U.S. approval (from sources outside the United States). Other drugs that were available in the U.S. market through an accelerated path but did not successfully meet payor needs may have many years of delay in creating pharmacoeconomic data for a reimbursed launch. Therefore, the reimbursed U.S. launch would be delayed and consequently the delay peak number of reports. In such cases, the FAERS will likely have very few cases reported after the initial market availability until full reimbursed launch.

1.2.1.3 Effect of publicity

Reporting may also be influenced by the product's advertising, which includes information on labeled ADRs and the publicity of specific ADRs (e.g., class action lawsuits, media attention, congressional sessions, and publications). For example, a textbook on pharmacovigilance states that "drug safety officers live in dread of reports of celebrities or politicians using a particular product, especially if an AE is reported" (Cobert, 2011). Increased media attention or other publicity noticeably increases the ADR report for the drug. This situation is referred to as the "secular effect" or "temporal bias." Reporting frequency is also influenced by the quality of the manufacturer or distributor's surveillance system.

1.2.1.4. Cannot estimate incidence

Rates of occurrence cannot be established from a SRS. The number of adverse events in the database cannot be used to determine the likelihood of a side effect occurring. Specifically, the denominator is unknown in a SRS. In theory, all patients who experience ADRs can and should report, and the total number of ADRs for a given drug is available; however, the total exposed population is unknown. It is challenging to detect delayed ADRs where it is difficult for reporters to suspect causality. Detecting ADRs in an environment with a high background incidence is also problematic. For example, feeling hungry is experienced by everyone with a variable frequency, and suspecting a causal relationship with a drug may be more unlikely than a visible skin rash following the administration of a drug.

1.2.1.5. Missing context

Certain clinical features tend to increase the chance that patients will experience ADRs: old age, neonates, women, renal impairment, underlying disease–drug pairs, polypharmacy, and a previous history of an ADR (Alomar, 2014). Such information, enabling detection of user-dependent safety, is often missing in the SRS as these are not required for a safety case report to be considered valid, as discussed earlier. These factors are particularly important for discriminating the intrinsic safety issues of a given drug compared to user-dependent safety. However, such discrimination is not the role of SRS. Rather,

the primary function of SRS is signal detection and hypothesis generation, which provides a starting point for analysis.

1.2.2. Strengths of SRS

The strength of a SRS lies in its simplicity, which also leads to its limitations. The simplicity allows for SRS's universal application to all drugs across time. Even with the evolution of PV systems, the database dating back half a century can still be integrated. The simplicity of SRS allows for rapid reporting of suspected ADRs without lengthy case investigation, interpretation, and narrative writing such as that needed in the evaluation of serious or other individual safety cases of special interest during a clinical trial. Indeed, unless the process is simple, busy healthcare professionals will be less likely to submit voluntary reports. The simplicity allows for the capturing of clinical suspicion that may otherwise be unreported.

1.2.3. Databases

The United States was the earliest to adopt an SRS. The U.S. SRS dates back to 1968, and the Adverse Event Reporting System (AERS) from 2000. AERS later changed its name to the FDA Adverse Event Reporting System (FAERS). The current FAERS database includes data from SRS and AERS.

The FAERS database is available to the public via an interactive web-based dashboard, with access to the FAERS data files. FAERS receives mandatory reporting from manufacturers, distributors, and packers, as well as voluntary reporting from consumers and healthcare professionals. In addition, FAERS collects structured information guided by the ICH E2B. The MedDRA coding system is used for AE nomenclature at the level of PT. Previously, the FDA used the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) in conjunction with Clinical Modification of ICD-9 (ICD-9-CM). The FAERS contains many free text items, including the drug name. No standardized drug nomenclature system is used. If the drug name is spelled incorrectly, the case will not be extracted with the correctly spelled name. Moreover, the FAERS database is not extensively sanitized. For example, if a patient's age entered is implausible, the case report still will not be discarded. Suspected duplicates will also not be discarded (FDA, 2018c).

Other AE databases often used in signal detection include the Vaccine Adverse Event Reporting System (VAERS), VigiBase, EudraVigilance, and the German spontaneous reporting database. The VAERS is the FAERS equivalent for vaccines maintained by the U.S. FDA and the Centers for Disease Control and Prevention. Like the FAERS, VAERS includes mandatory reporting from manufacturers, distributors and voluntary reporting from consumers and healthcare professionals. The AE and drug nomenclature are the same as the FAERS.

The WHO VigiBase is hosted and maintained by the Uppsala Monitoring Center with data sources from national centers (e.g., the U.S. FDA, UK Medicines and Healthcare Products Regulatory Agency, the German Federal Institute for Drugs and Medical Devices [*Bundesinstitut für Arzneimittel und Medizinprodukte*] [BfArM]). The VigiBase uses WHO-ART for AE coding and the WHO Drug Dictionary (WHO-DD) for drug nomenclature (Uppsala Monitoring Centre, n.d.).

EudraVigilance is the EMA system, including reports from manufacturers (including non-EU data) and European national centers, but not direct voluntary reports. Data that do not meet quality standards are rejected. MedDRA is used for AE coding and the proprietary name and the Extended EudraVigilance medicinal product dictionary (XEVMPD)(EMA, 2014) is used for drug coding (EMA, n.d.).

The German spontaneous reporting database maintained by the German health authority BfArM only includes domestic cases. Unlike the WHO Vigibase and EMA EudraVigilance, the German SRS receives voluntary reports, but only from consumers (not healthcare professionals) because healthcare professional reporting falls under mandatory reporting along with manufacturer requirements. Although the smallest of the databases mentioned above, routine data sanitation is performed on the German SRS and data

quality checks include checks for plausibility and duplicates. The German SRS uses MedDRA AE coding and WHO-DD drug coding.

1.3. Signal detection

Despite the limitations discussed above of using a SRS for safety analyses, these systems are essential in generating signals, especially in a broader patient population, including those excluded from clinical trials. SRS's main strength is in the detection of events not seen in clinical trials. Additionally, SRSs provide information on reporting trends, possible risk factors or risk populations, and emerging risks.

Randomization and the use of comparison groups make the interpretation of causation more straightforward. Observation studies provide evidence of association, not causation. Interpretation of potential causation in epidemiology generally considers chance, bias, and confounding factors. As discussed in the sections above, multiple systematic errors can occur from reporting bias, and confounding factors cannot be evaluated from FAERS data. Disproportionality analyses and cut-off criteria have been used to interpret that the observation is less likely to have been due to chance.

Postmarketing PV begins with signal detection. The Council for International Organizations of Medical Sciences (CIOMS) VII Working Group defined a

signal as “a report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance (CIOMS, 2021 pg 63).” The definition of a signal evolved in CIOMS IV to refer to “an event that may have a causal relationship” rather than “unknown causal relationship (CIOMS, 2021 pg 64).” Additionally, CIOMS VIII defined qualitative and quantitative signal detection. In qualitative signal detection, “The assessor uses his/her human intellect to evaluate the likelihood that the adverse event was caused by the suspect drug (CIOMS, 2021 pg 48).” Quantitative signal detection is defined as “statistical methods used to identify drug-event pairs (or higher-order combinations of drugs and events) that occur with disproportionately high frequency in large spontaneous report databases” (CIOMS, 2021 pg 48).

Signals have been particularly useful in identifying new risks, new at-risk populations, and extremely rare serious reactions. However, in the regulatory PV framework, not all signals are further processed. Those signals that will significantly alter a medicine’s benefit-risk profile will be prioritized and further evaluated. Once a signal is verified through a randomized clinical trial or formal verification studies, the clinical implication will be evaluated for potential label action.

1.3.1. Disproportionality Analyses

Disproportionality analysis was originally developed for spontaneous data (Hobbiger, 2013). Bate (2018) describes SRSs as lacking both a numerator and a denominator as not all cases of ADR are reported, and the exposure denominator is unknown. For this reason, SRS mining has analyzed reporting rates that differ from incidence rates. For this purpose, disproportionality analysis was developed to identify the imbalance in reporting of a particular ADR associated with a particular drug. Note that comparing risks in clinical trials is rather straightforward. Traditional epidemiologic methods using medical records also allow for incidence calculations. However, this is impossible for signal detection from SRS because exposure information is unknown and not all incident cases are reported.

In the past, denominator data on usage could be employed in an attempt to calculate incidence, for instance, using the number of prescriptions dispensed. However, the amount of the drug sold can be found, but how many patients took what percentage of the medication is uncertain. Also, spontaneous ADR schemes have a variable degree of under-reporting and are no longer widely used (Hobbiger, 2013). In addition, manufacturers have different rigor in training employees who may encounter ADRs, varying levels of patient contact (e.g., patient support programs) for the systematic collection of safety events, and different PV systems and processes. For example, after a disproportionality analysis of increased eating drives associated with atypical antipsychotics was published (Yum et al., 2021), only 1 of 5 manufacturers

contacted the authors to inquire about the safety signal. This occurred because these 5 companies have different processes (keywords, intervals, databases) for scanning the literature for new safety signals. This means that manufacturers and distributors who more diligently and proactively operate PV systems will have more ADRs reported for their drugs compared to companies that may apply less rigor in their PV systems, Therefore, employing usage denominators can make the former drugs appear to have a greater incidence of ADRs. Drug usage data can, however, still help provide some context for understanding the data.

For SRS mining in signal detection, the accepted method is to use differences in a particular ADR rate among all ADRs for a drug of interest against the rate for all other drugs in the database. Various classic and Bayesian methods have been developed, but they are all conceptually the same: detecting over-reporting of a particular ADR–drug pair to identify signals.

When all drugs are collectively considered, large ADR databases tend to have fairly stable proportions of particular ADRs over time. The basic concept behind “disproportionality” is whether or not more reports have been received for a particular drug-ADR pair than might be expected as background noise (Waller, 2017). Unlike formal pharmacoepidemiologic studies such as case-control or cohort studies that define a specified period of exposure, such time restrictions are not used in disproportionality analyses because they aim to

detect the emergence of a signal against a background rate that is stable over time as a collective comparator (i.e., the rate of a particular ADR reported for all drugs over time).

Frequentist or classical methods used to calculate disproportionality include the proportional reporting ratio (PRR) and the reporting odds ratio (ROR). The PRR is the rate of reporting of one specific event among all events for a given drug, the comparator being the reporting rate for all drugs present in the database. A disproportion is considered based on three pieces of information: PRR ≥ 2, $\chi^2 \geq 4$, and at least 3 cases (Evans et al., 2001). The ROR assesses one specific event versus all other events for a given drug compared to the reporting odds for all other drugs present in the database. A signal is considered when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one (Van Puijenbroek et al., 2002). The PRR and ROR formula and signal interpretation are summarized in Tables 1 and 2.

Table 1. Contingency table of drugs and events.

Drug	Adverse event of interest	all other AEs
Drug of interest	a	b
All other drugs	c	d

Table 2. Frequentist methods of disproportionality analysis.

Measure of association	Formula	Signal
Proportional reporting ratio (PRR)	$\frac{a/(a+b)}{c/(c+d)}$	PRR ≥ 2 and $\chi^2 \geq 4$ and N ≥ 3
Reporting odds ratio (ROR)	$\frac{a/(a+b)}{c/(c+d)}$	Lower limit of 95% CI > 1

Several methods exist for assessing whether the drug-event pair reports are disproportionately high enough to be deemed an association. In general, the frequentist methods PRR and ROR for disproportionality analyses have higher sensitivity but lower specificity compared to Bayesian calculations. However, frequentist or Bayesian methods are thought to perform similarly when there are five or more reports of a particular product-event pair (CIOMS, 2010).

1.4. Relatively benign soft ADRs

1.4.1. ABCDE Classification

Traditionally, in pharmaceutical medicine, there have been several ADR categorizations, based on severity assessment (generally for small molecules in conditions not immediately life-threatening), toxicity grades (mainly in oncologic drugs, biologics), seriousness (based on outcome), expectedness (e.g., SUSAR), suspicion of causality.

There is also an ABCDE classification. Type A (a.k.a. intrinsic, augmented) ADRS are predictable from pharmacology, are generally dose-dependent,

occur frequently, detected early in clinical development, associated with low mortality. Exaggerated therapeutic effects and off-target/secondary pharmacologic effects discussed above would fall under type A. Type B (a.k.a. idiosyncratic, bizarre) ADRs are not pharmacologically predictable, with no clear dose-dependent relationship, having uncommon incidence, not detected during clinical development, but postmarketing surveillance, and may be associated with high mortality. Type B factors may be a user-dependent ADR, for example, due to immune factors or genetic factors (NHS, 2013).

Type C (chronic requiring prolonged exposure such as osteonecrosis from bisphosphonates), D (delayed onset such as another primary cancer years after chemotherapy), E (end of use; seen with withdrawal of treatment) ADRs were categories developed later.

Type A reactions are common and thus picked up in development clinical trials. Type B reactions are rare and usually discovered from SRS signal detection processes.

1.4.2. Where do subjective patient experience ADRs fit in the ABCDE scheme?

Subjective patient experiences such as changes in hunger, appetite, food craving may be common intrinsic medication effects, but not picked up during clinical development, possibly because the implications are perceived as

benign, so not reported by the patient, or reported by the patient but not considered by the physician. Such subjective experiences may also be user-dependent, but very unlikely to be associated with high mortality. So, these experiences do not fit either type A or B in the traditional framework of a PV physician.

1.4.3. Patient drug experience and adherence

A drug is only effective when is appropriately administered. Physician discontinuation of a drug may be based on more serious ADRs such as drug-induced liver injury, cardiotoxicity, but patient discontinuation of drug discontinuation is often based on subjective discomfort.

In the clinic, patient self-discontinuation of medications may be due to ADRs that had much greater significance to the patients than physician expectations. For most ADRs, if its possibility and transient nature are explained to the patient at the time of the first prescription, patients tend to continue the medication until they return to the clinic for discussion. There are particular ADRs, however, that patients have little patience for and sometimes discontinue on their own before coming back for the next visit, for instance, erectile dysfunction (Higgins et al., 2010), or hair loss (Gupta & Masand, 2000). When weighing the severity of depression, neurovegetative symptoms and signs, or morbid wishes, then erectile dysfunction and hair loss may not be on a clinician's priority list. The importance of sexual function and

luscious hair on the patient's identity and self-esteem may be overlooked.

Weight is another such theme. Patients (except those with wasting diseases) often welcome weight loss as an ADR in a society that idealizes thinness. However, weight gain on a medication is not only unwelcomed but can even threaten the therapeutic alliance when unexpected or the magnitude of weight gain is visibly large (Dayabandara et al., 2017). Female patients for whom body weight and body shape constitute a significant portion of their self-esteem and identity might refuse to continue medications that suggest potential future weight gain, including those that seem to alter their hunger, appetite, and food craving.

In an investigation of diabetes medication adherence in 2,209 patients, 670 patients (33%) gained weight. The demographics, exercise habits, and dieting were similar between those who lost and gained weight. Medication adherence was significantly better in the group that lost weight (Grandy et al., 2013).

It is estimated that about half of the patients with diabetes are adherent to prescribed medication at 12 months. For example, a retrospective cohort study examining 1-year adherence on antidiabetic medicines using the U.S. MarketScan claims that in its database of 238,372 patients, 55.0% of DPP-4i initiators, 47.8% of SU initiators, and 42.9% of TZD initiators did not

discontinue therapy (Farr et al., 2014).

Treatment adherence is an established marker of prognosis in diabetes (García-Pérez et al., 2013; Polonsky & Henry, 2016). If weight gain leads to poor treatment adherence, then presumably, factors that may contribute to weight gain, such as increased drive and need to eat, might also lead to treatment noncompliance.

Although experiences that may be associated with patient self-esteem and self-identity, such as sexual function, hair loss, or increased food intake are not traditionally regarded as important considerations in regulatory pharmacovigilance systems, if these ADRs affect treatment adherence and thereby the effectiveness of medicines, it would be sensible for clinicians to be more vigilant in their monitoring.

The process of signal detection is fundamentally a proactive effort to minimize patient harm and maximize patient benefits. In this regard, subjective patient experiences should be an integral part of assessing the medication benefit-risk profile.

1.4.4. Examples of soft signals detected from SRS

SRSs have demonstrated the ability to detect seemingly benign patient

discomforts as signals. A historic example is captopril, which was first marketed in 1982. By 1986, there were 15 reports of cough in the UK SRS. The criteria for a signal were met 2 years earlier, but the signal was recognized after the association appeared in the literature (Waller, 2017).

A soft signal maybe a tip of an iceberg for more nocuous phenomena. A historic example of a soft signal that ultimately uncovered a drug safety disaster is practolol. As a beta-blocker used to treat hypertension and angina, practolol was later found to be associated with the oculo-mucocutaneous syndrome. The syndrome presents with relatively benign signs of dry eyes, skin rash, and bowel obstruction. A long latency of about 2 years made the signal difficult to detect. Once an association was reported in the medical literature (Wright, 1975), 3,000 cases were retrospectively reported to the UK pharmacovigilance database under the Yellow Card scheme. A fraction of the patients had profound visual loss and the medication was eventually withdrawn from the market. On a side note, practolol is a classic PV example that appears in educational materials for pharmaceutical physicians because after the association with a multi-system disorder was identified, efforts to create animal toxicity models failed. Therefore, nonclinical testing would not have predicted the safety issue (Waller, 2017). Hence, caution should be taken referring to an investigational medicine as “safe” based on nonclinical tox studies. Yet another example of non-hard safety issues identified from postmarketing SRS is a photosensitivity ADR with benoxaprofen (Routledge,

1998), in which too many reports overloaded the computer systems at the time (Waller, 2017).

1.5. Increased eating drive as an ADR

Weight gain that compromises medication adherence is an easily recognized ADR. Many clinical trials measure body weight as a part of the basic physical exam item to monitor. Weight is even measured in animal tox studies. Thus, much information is available about which drugs cause weight gain. Sometimes, particularly when the magnitude of weight gain is large, efforts are made to identify reasons for the weight gain. Such efforts focus on identifying quantifiable markers, most often laboratory markers. The amount of food eaten, or the frequency of eating and the number of calories consumed could also be quantified. Such quantification methods would be similar to how animal assays would be performed.

However, patients can provide individual narratives as well as their own observations and hypotheses. People can also provide information on whether their drives to eat have changed, such as needing or wanting to eat more. If the changes are troubling enough, they may report them to their physicians. If a high suspicion of drug relatedness is present, patients (who are familiar with the PV system) might directly report an SRS. The question therefore remains whether SRSs can detect changes in eating drives as signals. A search of the

literature did not yield an example.

1.5.1. Hunger, appetite, craving—wanting, liking, needing

Everybody feels hungry from time to time. However, what "hungry" means for each individual is highly variable. For some, it is a sensation brought on by lack of food or insufficient nutrition, as in the "world hunger problem." For some others, hunger means stomach contractions (a.k.a. hunger contractions) or growling after the stomach has been empty for several hours. For people that understand hunger as such a physiologic concept, it is thought to be an innate drive.

For some individuals, however, the sensation of hunger is not organic. Perceptual and conceptual errors exist as a result of learning. Psychotherapy of obesity attempts to correct the learned error and facilitate re-learning to differentiate hunger from other emotional tension. In a psychoanalytic understanding, hunger has a complex, symbolic meaning.

Hilde Bruch (1973) defined physiologic hunger as a state of nutritional depletion, food deprivation, or a result of starvation. She defined psychologic hunger as a complex, unpleasant, and compelling sensation which is experienced as a feeling of deprivation, searching, and fighting for food for relief (Bruch, 1973). Bruch differentiated hunger from appetite, the latter

defined as a more pleasant form, such as a desire for a particular food (Bruch, 1973).

The following is a description of a psychiatrist's operating model of hunger, appetite, and eating behaviors in the clinic. Based on psychoanalytic theories, a child learns to take care of itself throughout development, including feeding. The primary caretaker's appropriate responses to the child's needs allow the child to learn to differentiate hunger from other discomforts. The process of development (through interactions with others and the environment) also shapes the way a person views oneself, including self-esteem, interpersonal security, interoceptive awareness (including hunger), sense of effectiveness, sense of control (including appetite).

Biologically, a person is born with a set of genes and constitutional factors. Depending on which genes are expressed, numerous proteins are expressed that affect the neurocircuitry of various systems affecting cognition and behaviors. Sensory processing, autonomic nervous system reactivity, and the hormonal milieu are likely to be primarily biologic in their etiology, although psychosocial processing of external environmental stressors can also affect neurodevelopment. When external tension or conflict arises, a person may feel a "void" as described by Balint (1992), which might be individually perceived as hunger, emptiness, boredom, and more. This may lead to the Freudian concept of oral regression, where the individual consumes in excess like a

vacuum, leading to symptomatic manifestations, such as overeating. This may be followed by efforts to get rid of the excess, such as purging (vomiting, compensatory exercise, fasting, laxatives, diuretics, diet pills) and other undoing behaviors. Some may opt for genital regression manifested in various excitement seeking (extreme sports, violence, sex, drugs, palatable foods). When the conflict is not resolved, one may seek a route of escape, such as denial, projection, or displacement. Alternatively, conflict may resolve, and the self assimilates or accommodates the experience. This process is simplified in the **Figure 2**.

Figure 2. A simplified model of psychological hunger.

Modified (simplified) from Yum et al. (2009, p. 23).

In psychiatric patients, subjective distress related to life stressors predicted less control over food intake and greater experience of hunger. The associations were stronger in the obese and overweight groups. Psychiatrist rated objective measures of psychopathology did not predict disinhibited eating or subjective hunger (Yum, 2005a).

After having discussed the various meaning of *hunger* for individuals, psychological void or emotional tension states perceived as hunger are probably unlikely to be reported as an ADR unless the drug is depressogenic, or anxiogenic, as those patients that report to SRSs have been shown to generally attribute causation to temporality (Krska et al., 2011).

Bruch (1973) described appetite as a pleasurable anticipatory desire, for a specific food or food feature. However, in everyday language, appetite and hunger are used interchangeably. Craving is also used to mean appetite. Craving in psychiatry is more of a need (not want, like) as a result of addiction to avoid the discomforts of withdrawal. As an ADR, increased appetite, if used precisely, may be a sign of anhedonia or blunting of pleasure (e.g., antidopaminergic drugs) where the patient continues to desire the pleasure that has been reduced. Food craving as an ADR, if used precisely, could be a withdrawal symptom of an appetite suppressant or a response to hypoglycemia (or relative hypoglycemia).

In reality, hunger, appetite, and food craving are used interchangeably in daily conversations, so a SRS is unlikely to have precisely captured the different phenomena. Instead, these terms collectively could provide a signal for whether a medication might be increasing eating drives.

1.6. Diabetes, antidiabetic drugs and the drive to eat

The goal of diabetes treatment is to reduce mortality and morbidity, in particular target organ disease. Disordered eating behavior is reported to be associated with a threefold increase in diabetic retinopathy during a 4 year follow-up period and eating disorders were more predictive of retinopathy than the duration of diabetes (Rydall et al., 1997), which is established as a major risk factor for microvascular complications.

1.6.1. Glucostatic theory

Since the presentation of the classic glucostatic theory, much debate has occurred with regards to the role of glucose in inducing hunger and satiety. The glucostatic theory suggested that decrease and increase in glucose use in critical brain areas respectively lead to increase and decrease the perception of hunger; this was thought to be the mechanism behind short-term control of hunger and food intake, while lipostatic mechanism accounted for long-term regulation of energy balance (Mayer, 1953).

The role of glucose in the perception of hunger and satiety is now thought to be more complex. The glucodynamic theory proposes that it is the dynamic change in glucose that leads to food intake rather than the statically defined glucose level (Bray, 1996). In free-feeding rats, a decline of 6-8% in blood glucose led to meal onset in about 5 minutes (Louis-Sylvestre & Le Magnen, 1980). Similarly, people perceived hunger and initiated meals with about a 10% decline in glucose (Campfield et al., 1996).

Patients with diabetes were observed to ingest, on average, 25% more energy during euglycemia compared to their hyperglycemic states (Schultes et al., 2005). This raises the question of whether therapeutic interventions, when quickly lowering glucose levels can lead to increased perception of hunger and consequent food intake.

1.6.2. Food addiction and diabetes

Diabetes, as well as obesity, were long believed to be willpower conditions. There are anecdotal cases among neighbors, workplace, family members, friends who boasted overcoming blood sugar with diet and exercise. Such people are praised for their perseverance and others are encouraged to follow or disparaged for their inability to do so. Is it the patient's lack of willpower that is the problem?

When the concept of food addiction first appeared, it was difficult to accept that something necessary for survival would be addictive. It was also difficult to conceptualize eating, which can be adaptive even when done excessively to help people cope with stressors and function, as being something similar to drug addiction, which is more often completely maladaptive, burning all social relationships, leading to problems at work, financially, and legally.

The research trend in food addiction started with media attention on imaging of the reward pathways in the obese that was replicated under various presentations of food stimuli. To be more precise, these pathways do not determine the resulting hedonic valence (reward) from food intake, but rather are involved in the motivational salience in anticipation of food, which is likely influenced by past hedonic valence experienced. Food intake is not a function of motivational salience alone but is influenced by physiologic signals from organs such as the liver, pancreas, adipose tissue, adrenal gland, hypothalamus that gets integrated in the brain. It additionally is influenced by positive social contexts like family gatherings, and celebrations as well as salient food features such as smell, plating (Yum et al., 2009).

Drugs of addiction, in comparison, are influenced by more negative contexts, such as illegal dealings in often dangerous environments, not motivated by

salient features but rather by negative consequences of withdrawal and the need to relieve associated agony.

Many psychiatrists' disease models are incompatible with the concept of overeating, binge eating, and other eating disorders as forms of addiction. The medical community, however, has slowly accepted this concept over the years. Endocrinologist Robert Lustig campaigned for the increased acceptance of seeking sugary, processed foods as a form of addiction through books, social media, and speeches to medical societies and the public. In his book *The Hacking of the American Mind*, Lustig presented arguments that sugar and processed foods (which are in large part sugar) are toxins that cause addiction and lead to diseases such as diabetes (Lustig, 2018).

The Yale Food Addiction Scale identified that certain types of foods might be addictive. The scale is based on the DSM-IV substance dependence criteria, identifying those who develop symptoms of dependence such as tolerance, withdrawal, and persistent desire (Gearhardt et al., 2009). This characterization contrasts with concepts of eating addiction in which the behavior is the problem, not the food (Mercer & Bird, 2012).

Although it is difficult to accept "food" addiction as a concept, it seems possible that certain foods and what was added to the food can be addictive. In my clinical experience, preference for palatable foods predicted

disinhibited eating in restrained eaters (Yum, 2005b) and disinhibited eating, in turn, was associated with metabolic disturbances (Yum, 2005a).

Animal studies have demonstrated sugar to be more addictive than cocaine or heroin (Lenoir et al., 2007; Madsen & Ahmed, 2015). Fructose shuts down IRS-proteins and PI3K resulting in insulin resistance, hyperphagia (Shpakov et al., 2015).

In his latest book, *Metabolical*, Lustig questions the types of food people are overeating in the modern age, which are not vegetables, legumes, fruits. He argues it is what has been done to the food (processing, additives) that make them addictive, causing insulin overdrive, which then leads to leptin resistance, mimicking starvation, causing hunger and craving for processed foods, and hence the vicious cycle (Lustig, 2021).

1.6.3. Biologically driven to eat more

Given the sugar and processed food-de novo lipogenesis in the liver-fatty liver-diabetes-insulin resistance-leptin resistance-mimicking starvation-hunger and craving relationship, diabetes itself is a condition that increases eating drives. When insulin worsens leptin resistance, then what do drugs that modify insulin signals do to drives to eat?

1.7. Research question: antidiabetic drug—increased eating drives explored with FAERS data

For patients with diabetes, adherence to the prescribed ways of living (i.e., diet and exercise) is just as important as compliance with prescribed anti-diabetic drugs (ADD). In the clinic, patients often disclose increasing difficulties in sticking to healthy diets, due to increases in hunger or appetite or lack of fullness or its maintenance. Sometimes, these disclosures are temporally associated with changes in the ADD regimen. And thus arises the clinical question whether different antidiabetic agents might differentially affect physiologic and appetitive or motivational aspects of feeding. A better understanding of how medications affect feeding may lead to strategies to optimize 24-hour glycemic control.

Regarding ADD-induced weight gain, one Cleveland Clinic endocrinologist said “I hate to give my patients these medications. I tell them to lose weight, and then I write a prescription that increases their appetite or makes them gain weight. It’s like shooting them in the foot” (Cleveland Clinic, 2018).

The questions posed in the conception of this study were twofold: (1) do ADDs affect eating drives? and (2) Can an SRS, more specifically, the FAERS, detect signals of increased eating drives as ADRs?

2. METHODS

2.1. Source of spontaneous report database

2.1.1. FAERS

The FAERS database was mined for eating-related symptoms for 6 anti-diabetic drug (ADD) classes, which included 15ADDs (FDA, 2021a). FAERS data sources include mandatory global reporting from manufacturers and distributors as well as voluntary reporting by consumers and health professionals. ADRs in FAERS are coded according to the standardized terminology of MedDRA at the level of a PT in its hierarchical classification. The FDA FAERS Public Dashboard was used for the extraction of AE reports until December 31, 2020.

2.1.2. Characteristics of individual case safety reports in FAERS

To present the characteristics of ICSRs (such as demographic features of the patients and the reporter characteristics) in the FAERS, a separate extraction was performed on June 6, 2021. The FAERS Dashboard confirmed that all cases until Mar 31, 2021 were included. FAERS is updated quarterly. ICSR characteristics including seriousness, reporter type, report region, and sex are presented in **Table 3**.

Table 3. Report counts in the FAERS in 2001–2010 and 2011–2020 by seriousness, reporter type, report region, sex: case report numbers and within-category proportions.

		2001–2010	2011–2020	2001–2010/ 2011–2020
Total reports		3,510,903	15,799,736	4.5
Seriousness	serious	2,257,898 64.31 %	8,292,352 52.48 %	3.67
	death	433,262 12.34 %	1,479,056 9.36 %	3.41
	non-serious	819,743 23.35 %	6,028,328 38.15 %	7.35
Reporter type	HCP	1,742,825 49.64 %	7,942,130 50.27 %	4.56
	consumer	1,196,139 34.07 %	7,653,029 48.44 %	6.39
	missing or other	571,939 % 16.29 %	204,577 1.29 %	0.36
Report region	United States	2,319,616 66.07 %	10,794,433 68.32 %	4.65
	out-of-USA	1,180,084 33.61 %	4,996,370 31.62 %	4.23
	missing	11,203 0.32 %	8,933 0.06 %	0.80
Sex	women	1,923,696 54.79 %	8,585,274 54.34 %	4.46
	men	1,313,694 37.42 %	5,432,037 34.38 %	4.13
	missing	273,513 7.79 %	1,782,425 11.28 %	6.52

HCP: healthcare provider.

As of the first quarter of 2021, a total of 22,002,078 case reports were in the database, reports dating back to 1968. Among the total reports, 55.57% of the cases (12,226,890) were reported for serious outcomes excluding death, and 9.7% of the total reports (2,112,304) were associated with death.

Table 3 presents reporting frequencies by categories (seriousness, reporter, report region, sex) for the last 10 years and the 10 years preceding. The volume of ICSRs has increased by 4.5-fold in the past decade compared to the decade before. The annual distributions of these categories and additionally age distribution over the years during the existence of the database are shown in **Figures 3-7**.

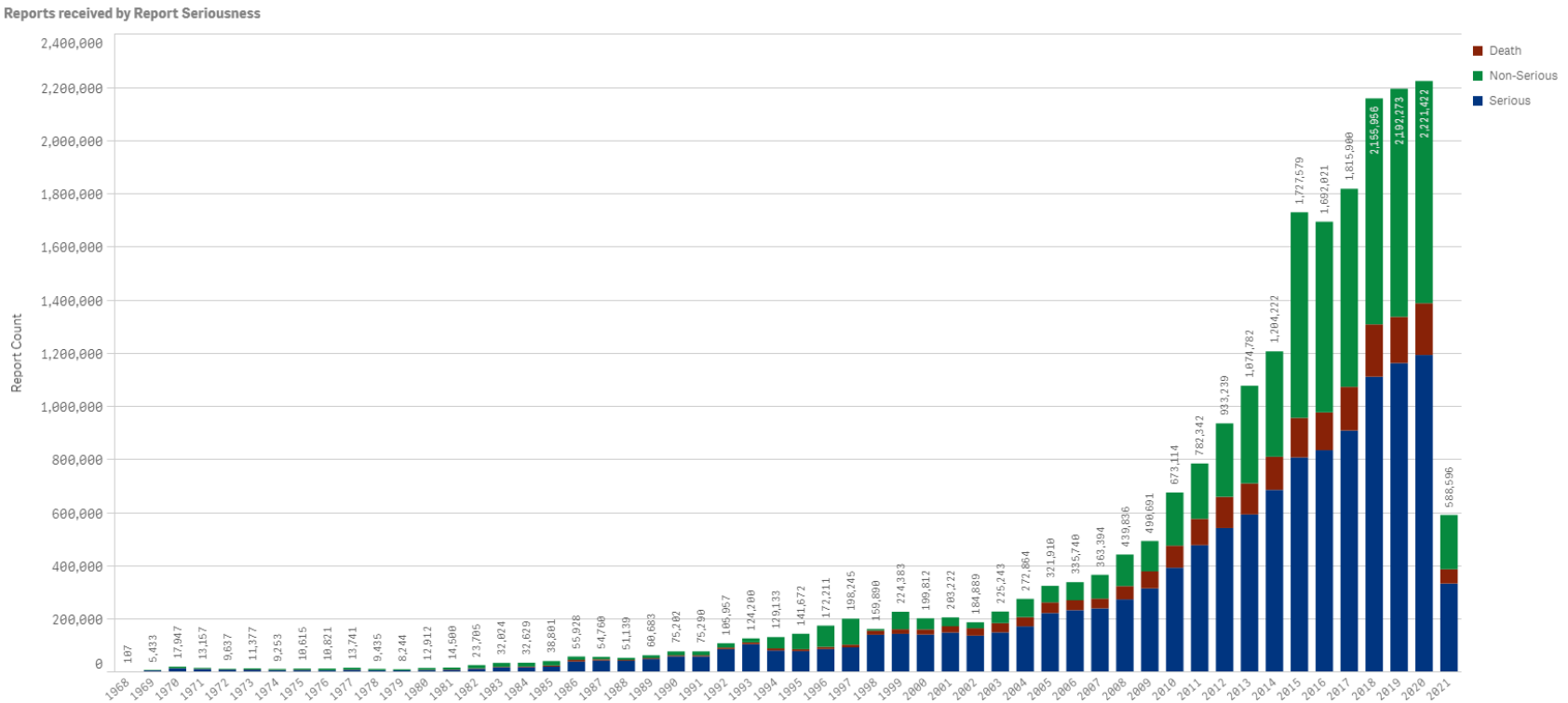

Figure 3. Report counts in FAERS over years from 1968 to June 2021 by seriousness.

The seriousness of the cases (non-serious, serious, death) is separately displayed in different colors. The annual report counts have increased over the years. The database has collected increasing proportion of non-serious reports in the past few years. (Graph extracted directly from the FAERS platform.)

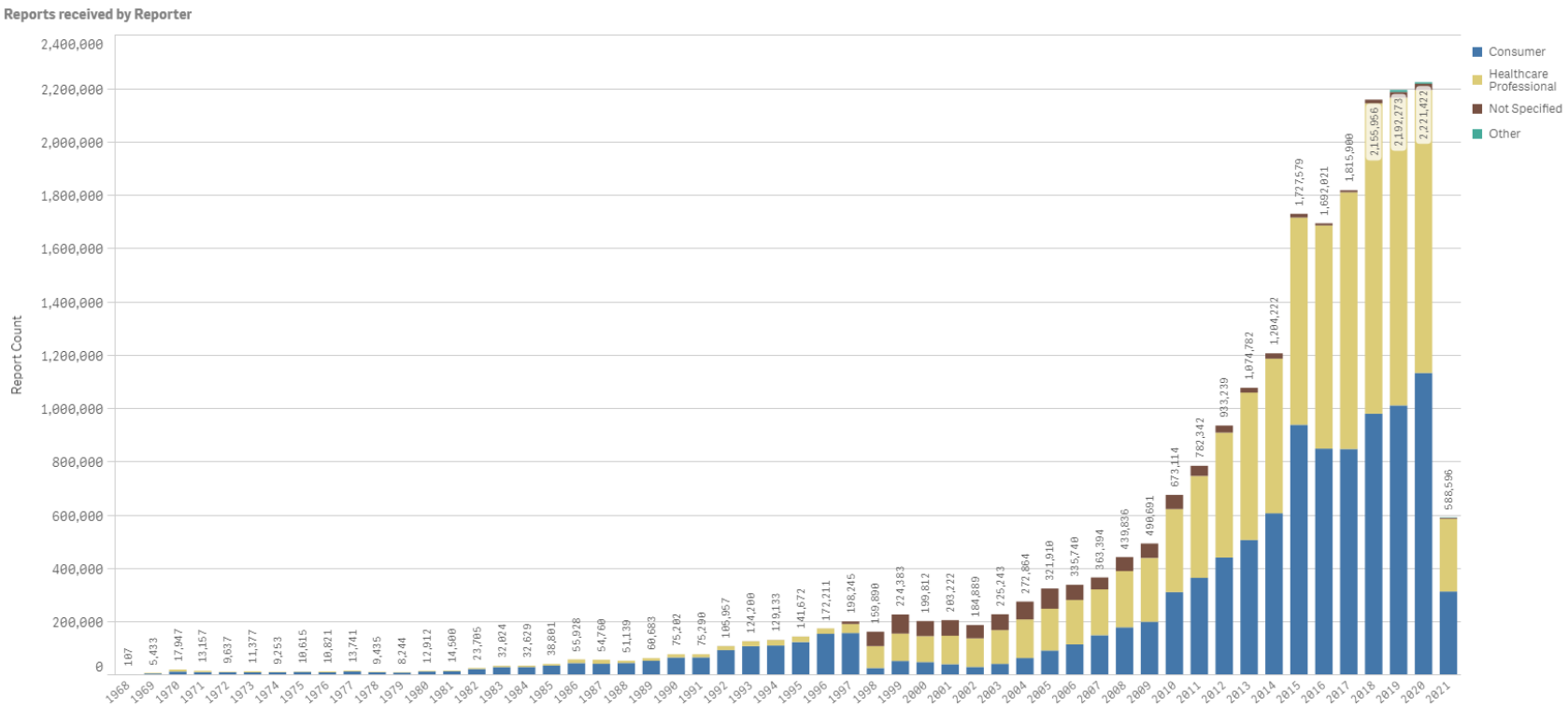

Figure 4. Report counts in FAERS over years by reporter type.

Reporter types (consumer, healthcare professional, not specified, other) are separately displayed in different colors. Both consumers and healthcare providers are reporting more ADRs to the SRS in recent years, the trend more notable in healthcare providers. (Graph extracted directly from the FAERS platform.)

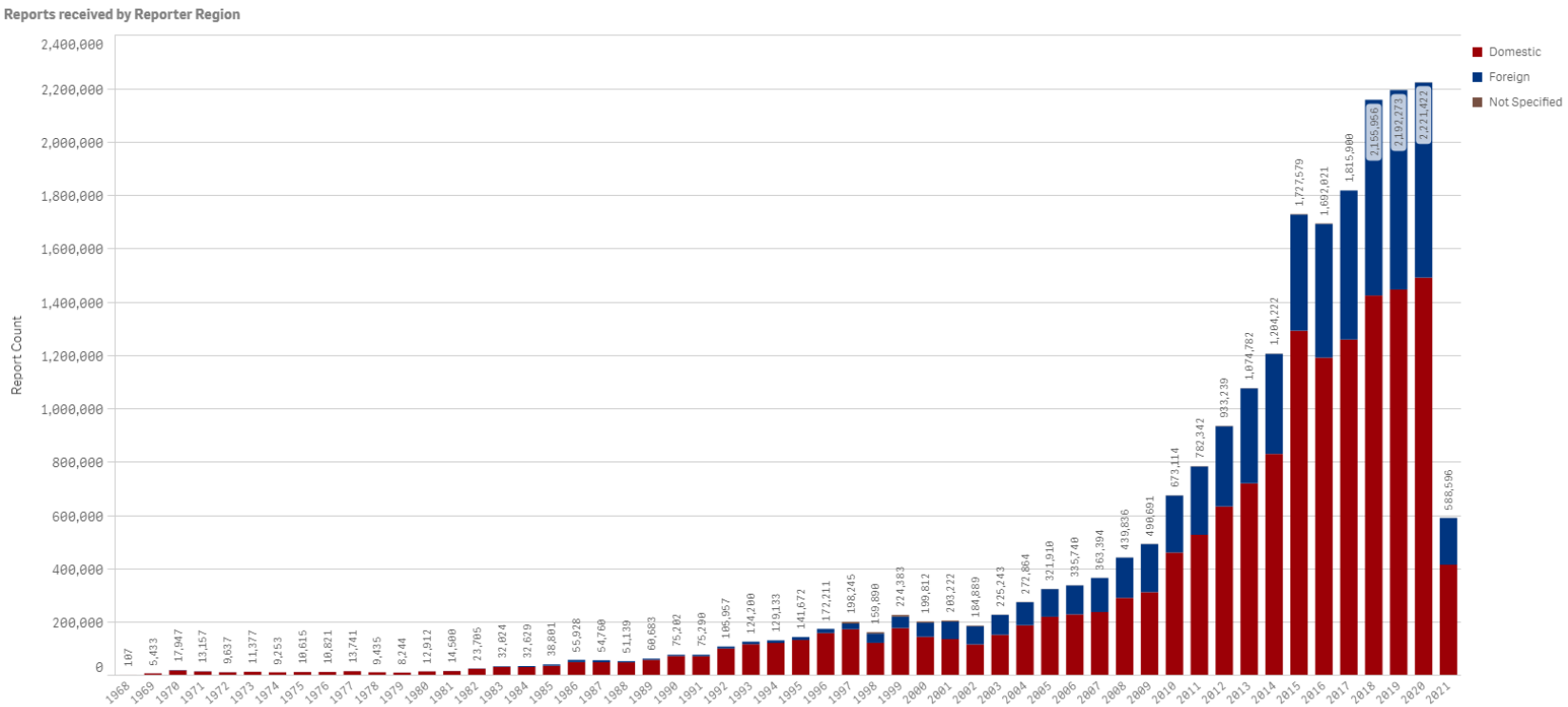

Figure 5. Report counts in the FAERS over the years by reporter region.

Reporter regions (USA, out-of-USA) are separately displayed in different colors. The majority of case reports are received from the United States but increasing number of reports are also received from outside the United States. (Graph extracted directly from the FAERS platform.)

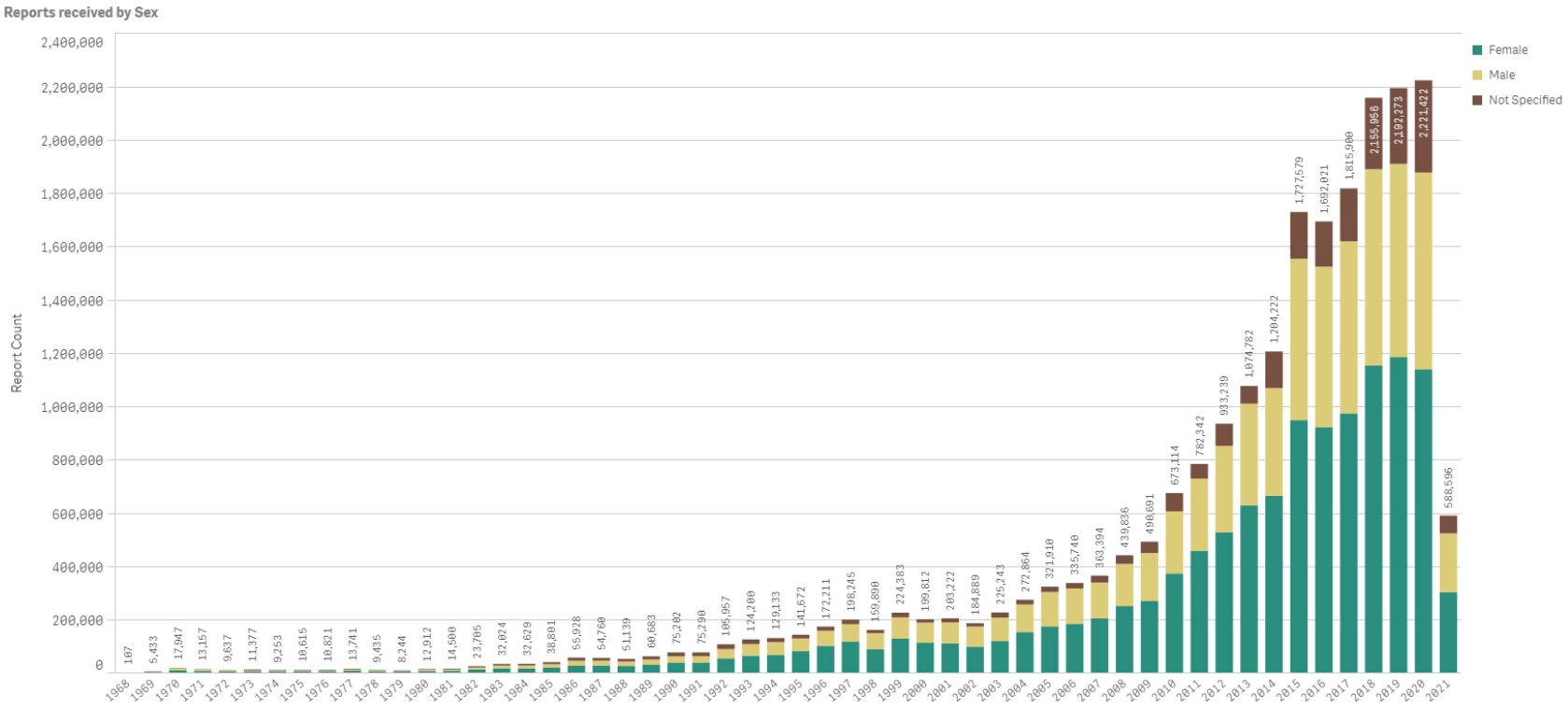

Figure 6. Report counts in the FAERS over the years by sex

Sex distribution (man, woman, not specified) of cases are separately displayed in different colors. (Graph extracted directly from the FAERS platform.)

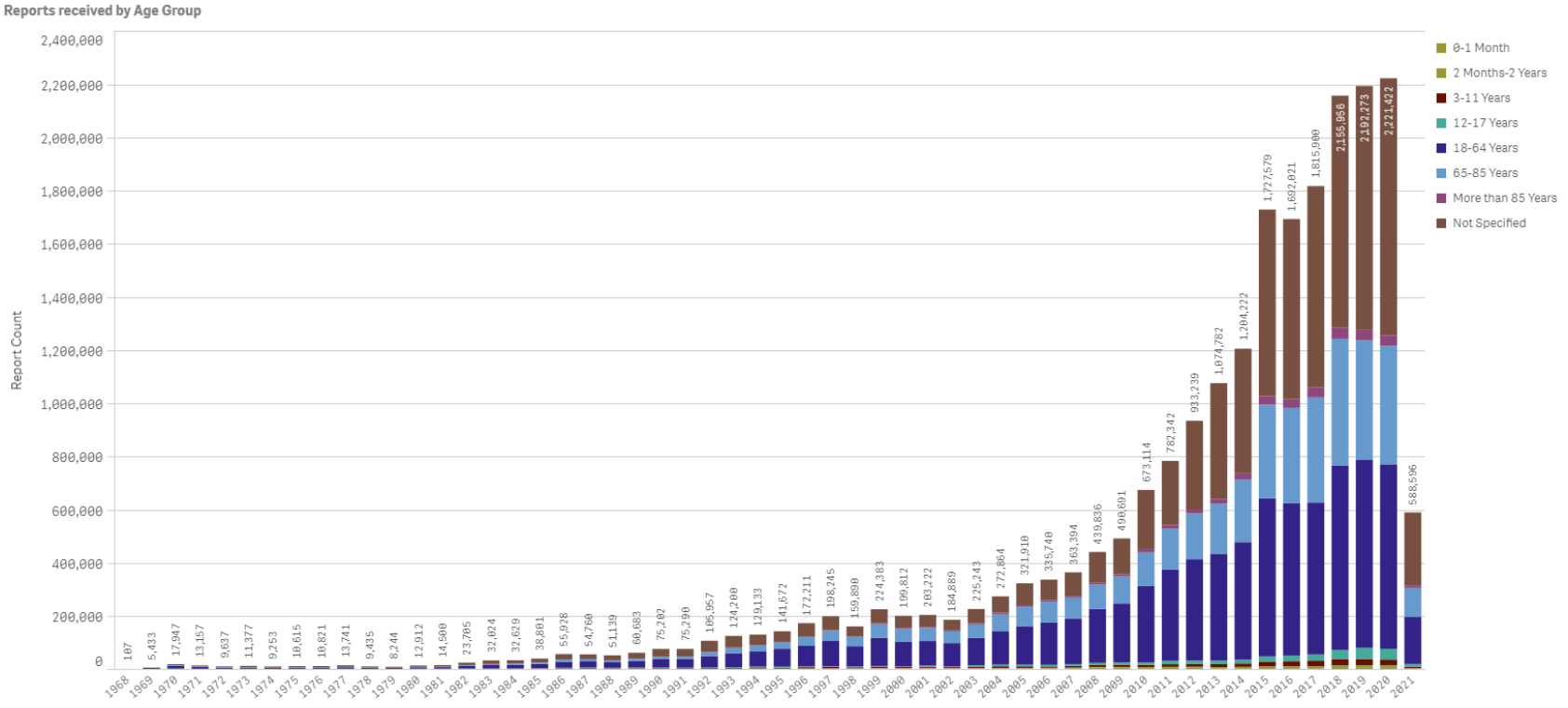

Figure 7. Report counts in FAERS over years by age (Graph extracted directly from the FAERS platform.)

2.2. Reaction terms examined

2.2.1. ADD-increased eating drives

MedDRA PTs relating to hunger and appetite were used as drug reactions of interest. These included: *hunger*, *increased appetite*, and *food craving*. Despite their distinct neurobiology, because hunger and appetite are often used interchangeably in daily language, the first 3 PTs were added for an additional aggregate signal of "increased eating drives." The consequent behavioral output was examined using *hyperphagia* as an AE term. Lastly, *weight increased* was used to see if signal patterns are consistent with increased eating drives and behavioral output.

Hunger as a PT falls under the SOC *general conditions.* The PTs *food craving*, *increased appetite*, and *hyperphagia* are under *metabolism and nutrition disorders.* The PT *weight increased* belongs to *investigations* SOC.

Of the 20,484 PT level event terms, a total of 55 PTs were thought to be possibly related to changes in eating drives, and eating behaviors. The SOC and PTs are listed below in **Table 4**.

Table 4. List of all potential event terms

SOC	PT
General Disorders and Administration Site Conditions	*Diet Failure*
	Early Satiety
	Fat Tissue Decreased
	Fat Tissue Increased
	Hunger
Investigations	Body Mass Index Abnormal
	Body Mass Index Decreased
	Body Mass Index Increased
	Carbohydrate tolerance decreased
	Carbohydrate tolerance increased
	Waist Circumference Increased
	Weight Abnormal
	Weight Decreased
	Weight Increased
Metabolism and Nutrition Disorders	Abnormal Loss Of Weight
	Abnormal Weight Gain
	Appetite Disorder
	Body Fat Disorder
	Bradyphagia
	Carbohydrate intolerance
	Central Obesity
	Decreased Appetite
	Diet Refusal
	Eating Disorder Symptom
	Fat Redistribution
	Feeding Disorder
	Feeding Intolerance
	Food Craving
	Hyperphagia
	Hypophagia
	Increased Appetite
	Obesity

	Overweight
	Refeeding Syndrome
	Salt Craving
	Starvation
	Underweight
	Weight Fluctuation
	Weight Loss Poor
Psychiatric Disorders	Anorexia Nervosa
	Binge Eating
	Disinhibition
	Eating Disorder
	Fear of Eating
	Fear of Weight gain
	Selective Eating Disorder
Social Circumstances	*Diet Noncompliance*
	Inadequate Diet
	Unhealthy diet
Surgical and Medical Procedures	Low carbohydrate diet
	Low fat diet
	High carbohydrate diet
	High fat diet
	Weight Control
	Weight Loss Diet

All event terms that could be considered to broaden the search for all possible cases of changes in eating drives, behaviors and consequent outcome; those potentially relevant to increased eating drives are italicized; final selections are bolded and italicized

If the purpose of this project was to detect any possibilities for the ADDs to cause changes in eating drives, the entire list of PTs in the table above could have been used. Alternatively, the PTs can be classified and tested sequentially by increasing certainty in terms of possible, probable, most likely capturing

the increase in eating drives.

For example, the terms *unhealthy diet, inadequate diet, diet noncompliance* may have been reported by the physician for patients who indulge in sweet desserts, sugary drinks, or excessive portion sizes. This may have been due to hunger, sweet craving, voracious appetite, or behaviors for which the patient had no cognitive awareness of the reason. But these could also have nothing to do with increase in eating drives, but rather due to social circumstances influencing the availability of food types. Without contextual information, these PTs cannot be interpreted.

The project's purpose was to explore whether subjective patient distress, dissatisfaction with drugs are also reported in significant amounts to the FAERS to enable signal detection. Therefore, only AEs with a high level of certainty that can be taken at face value to mean increased eating drives were used.

Two PTs that were considered and not selected for extraction are *binge eating* and *disinhibition*. If the disinhibition had an eating specifier, that is disinhibited eating, it would have been selected. But what is disinhibited (emotion, behavior, thoughts, speech) is unknown. *Binge eating* for a non-psychiatrically trained person probably means an exaggerated version of overeating. However, in the MedDRA, it is classified under the SOC

psychiatric disorders. For a psychiatrist, a binge eating episode requires 2 things: (1) objectively large amounts of food are consumed quickly, and (2) a subjective sense of loss of control (APA, 2013).

Patients often think of the loss of control in an addiction framework as in loss of ability to resist, which is associated with the initiation phase of eating, or the continuation phase. A binge observed in binge eating disorders and bulimia nervosa or anorexia nervosa binge-purge subtype is a disorder of the termination of eating. Patients describe gulping down piles of pastry while crying due to physical pain of gastric distension but still unable to stop, and pain is alleviated momentarily with swallowing. These episodes invariably are preceded by periods of fasting or highly restrictive diets, so likely the phenomenon is a result of disinhibition. Although it would be of interest to patients to explore whether ADDs can contribute to the disinhibition or worsen binges, it was expected that *binge eating* coded under SOC *psychiatric disorders* would be more likely associated with cases of psychiatric definitions rather than increased drives to eat (more specifically initiate eating) which is the ADR of interest in this research. So, this particular PT was not included.

2.3. Drug names

2.3.1. ADD-increased eating drives

Six classes of ADDs were defined based on U.S. ADD prescribing pattern analyses (Montvida et al., 2018) of first- and second-line non-insulin agents: metformin, dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon-like peptide 1 receptor agonists (GLP1RA), sodium-glucose cotransporter 2 inhibitors (SGLT2i), sulfonylureas (SU), and thiazolidinedione (TZD). Fifteen non-insulin, single-agent ADDs that had the highest number of prescriptions in the United States were used for the extraction of drug-event pairs (Kane, 2020). Generic names of drugs were used for extraction. The following search terms (in italics) were used:

- *metformin hydrochloride*
    - first global approval: 1960
    - U.S. approval: 1995
- DPP4i
    - *linagliptin*
        - first global approval: 2011
        - U.S. approval: 2011
    - *saxagliptin hydrochloride*
        - first global approval: 2009
        - U.S. approval: 2009
    - *sitagliptin phosphate*
        - first global approval: 2006
        - U.S. approval: 2006
- GLP1RA

        - *dulaglutide*
            - first global approval: 2014
            - U.S. approval: 2014
        - *exenatide*
            - first global approval: 2005
            - U.S. approval: 2007
        - *liraglutide*
            - first global approval: 2009
            - U.S. approval: 2010
        - *semaglutide*
            - first global approval: 2017
            - U.S. approval: 2017
- SGLT2i
        - *canagliflozin*
            - first global approval: 2013
            - U.S. approval: 2013
        - *dapagliflozin propanediol*
            - first global approval: 2012
            - U.S. approval: 2014
        - *empagliflozin*
            - first global approval: 2014
            - U.S. approval: 2014
- SU:

- *glimepiride*
    - first global approval: 1995
    - U.S. approval: 1995
- *glipizide*
    - U.S. approval: 1984
- *glyburide*
    - U.S. approval: 1984

- TZD
    - *pioglitazone hydrochloride*
        - first global approval: 1999
        - U.S. approval: 1999

2.4. Disproportionality analyses

For signal exploration, greater sensitivity was opted for, and the reporting odds ratio (ROR) was calculated for each drug-event pair; drug adverse reaction signal was considered when the lower limit of the 95% confidence interval exceeded 1. The formula is described in **Tables 1 and 2** in Section 1.3.1.

2.5. Ethical statements

As the study mined a publicly available database with no sensitive

information, an exemption status was granted from the institutional review board of the Seoul National University Hospital (review number E 1406-093-589). The exemption request included the proposal to mine various cognitive, affective, and behavior adverse events in the FAERS system.

3. RESULTS

3.1. All cases for all drugs in the FAERS

A total of 24,047 case reports of hunger, food craving, and increased appetite were in the database until Quarter 1 of 2021, dating back to 1968. A total of 14,670 cases of increased appetite, 7,414 cases of hunger and 2,588 cases of food craving were reported as adverse reactions.

Consumers reported 69.33% (16,672) of the cases for increased eating drives, while healthcare professionals reported 23.94% (5,756). Reporter information was missing for 6.70%. For women, 64.80% (15,583) of the cases were reported, and 27.79% (6,682) of cases were reported for men. In addition, 7.41% of the case reports had “sex” as a missing field.

Of the 17,469 case reports where the country of reporting was available, 79.5% (13,888) were reported by the United States, followed by 817 cases from Canada, 743 from Great Britain, 327 from Brazil, 227 from Germany, and 195 from France. In Asia, 169 cases were from Japan, 43 from China and 13 cases were from Korea.

A total of 2,723 case reports of *hyperphagia* were in the database, with 60.48% (1,647) of the cases for hyperphagia reported by consumers, and 33.97% (925) by healthcare professionals. Women reported 56.08% (1,527) of cases, and 36.87% (1,004) cases were reported for men. Additionally, 7.05% of the case

reports had “sex” as a missing field.

A total of 173,561 cases reports of *weight increased* were in the database. Consumers reported 61.21% (106,245) of the cases for weight increase, and 32% (55,532) were reported by healthcare professionals. There were 11,737 cases in which the reporter type was missing, and 47 cases where the reporter field was “other.” Women reported 66.14% (114,797) of cases, and 26.71% (46,364) of the cases were reported for men. Moreover, 7.14% of the case reports had “sex” as a missing field.

3.2. ICSR characteristics of ADD classes

The reporter distribution and sex distribution of the ICSRs for each ADD class are presented in **Table 5**. For the aggregate events of increased eating drives, reports were more frequently received from consumers than HCPs for all classes of ADDs as well as the total FAERS database. For all ADDs as well as the total FAERs cases, women reported increased eating drives more frequently than men, except all ADRs for SGLT2i in which the proportions were similar, but slightly higher for men. For all ADRs, associated with ADDs, HCP report proportions were higher except for GLP1RA, for which 71.85% of all ADRs were reported by consumers.

For increased eating drive ADRs associated with GLP1RAs, 89.70% of the reports were received from consumers. The GLP1RA reports were different from other ADD classes in that there were more non-serious reports than

serious reports. Of the total ICSRs, 9.29% were non-serious cases for metformin, 37.55% for DPP4is, 39.54% for SGLT2is, 8.59% for SUs, 4.79% for TZD, but 72.08% for GLP1RAs.

For the GLP1RA ICSRs, 53.17% of the serious excluding death cases (20,631 reports) were reported by HCPs and 46% (17,850 cases) by consumers. For the non-serious cases, 80.83% (90,218 cases) were reported by consumers and 18.65% (20,819 cases) by HCPs.

Table 5. Reporter and sex distributions of all events and increased eating drives by antidiabetic class and all drugs in the database (greater proportions are bolded).

Drug		reporter			Sex		
		Consumer	HCP	Missing or other	Women	Men	Missing or other
		(%)	(%)	(%)	(%)	(%)	(%)
All drugs	all events	10,529,335	10,498,238	960,051	11,921,175	7,698,778	2,382,125
		47.89	47.75	4.37	**54.18**	34.99	10.83
	increased eating	16672	5756	1619	15583	6682	1782
		69.33	23.94	6.73	**64.80**	27.79	7.41
metformin	all events	24,481	56,694	3,904	41,908	33,787	9,384
		28.77	**66.64**	4.59	**49.26**	39.71	11.03
	increased eating	139	48	5	129	50	13
		72.40	25.00	2.60	**67.19**	26.04	6.77
DPP4i	all events	13,151	24,176	2,826	18,710	16,742	4,701
		32.75	**60.21**	7.04	**46.60**	41.70	11.71
	increased eating	66	44	14	79	33	12
		53.23	35.48	11.29	**63.71**	26.61	9.68
GLP1RA	all events	108068	41450	895	86907	56556	6950
		71.85	27.56	0.60	**57.78**	37.60	4.62
	increased eating	1742	192	8	1407	498	37
		89.70	9.89	0.41	**72.45**	25.64	1.91
SGLT2i	all events	15,564	29,504	159	19,716	20,445	5,066
		34.41	**65.24**	0.35	43.59	**45.21**	11.20
	increased eating	117	44	2	95	56	12
		71.78	26.99	1.23	**58.28**	34.36	7.36
SU	all events	12319	13398	2802	12444	12930	3145
		43.20	**46.98**	9.83	43.63	**45.34**	11.03
	increased eating	91	15	18	71	40	13
		73.39	12.10	14.52	**57.26**	32.26	10.48
TZD	all events	7181	9174	3974	5783	7273	7273
		35.32	**45.13**	19.55	28.45	**35.78**	35.78
	increased eating	23	11	34	44	23	1
		33.82	16.18	50.00	**64.71**	33.82	1.47

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione, HCP: healthcare provider

Consumers reported more increased eating than HCPs; women reported more increased eating than men for all ADD classes.

3.3. Disproportionality analyses

Contingency tables and disproportionality analyses of AEs associated with ADD classes are presented in **Figures 8-9**. Results for individual ADDs are presented in **Figures 10-15**. A heat map summary of disproportionality calculations is presented in **Table 6**.

Using the definition of a positive signal defined in Section 2.4, as presented in **Figure 8**, *hunger* and *increased appetite* were positive safety signals for all classes of ADDs. *Food craving* was a safety signal for metformin, DPP4is, GLP1RAs, and SGLT2is but not for SUs and TZD. The event numbers for SUs and TZD were low, resulting in wide ROR CIs. Taken together, the aggregate query for increased eating drives (sum of *hunger, food craving*, and *increased appetite*) yielded positive safety signals for all ADD classes. In addition to the motivational aspects, the behavioral output of increased eating, *hyperphagia*, also yielded positive signals for all classes of ADDs (**Figure 9**). *Weight increased*, which can be a physical or metabolic consequence of increased eating, was disproportionately associated with all ADD classes except SGLT2is (**Figure 9**).

Hunger was disproportionately associated with each of the individual ADDs (**Figure 10**). Within class heterogeneity in disproportionality signals was observed for *food craving;* among the DPP4is, sitagliptin yielded a positive signal, whereas linagliptin and saxagliptin did not. None of the SUs were disproportionately associated with *food craving* although the trend in

imbalance was in both directions among the different drugs within the class (**Figure 11**). *Increased appetite* was disproportionately associated with all ADDs in the biguanide, GLP1RA, SU, TZD classes. Within-class heterogeneity was observed again for DPP4is (**Figure 12**). The aggregate query for increased eating drives yielded positive signals for all individual ADDs except saxagliptin. Saxagliptin which had the fewest reports of increased eating drives also had the fewest total ICSRs among the ADDs; the ROR was 1.95, and the lower margin of the 95% CI was 0.96, showing a trend in disproportionality (**Figure 13**). Saxagliptin was the only DPP4i that was not disproportionately associated with an increase in motivation to eat, but it was the only DPP4i that was disproportionately associated with the behavior of increased eating, *hyperphagia* Additionally, SU glyburide which had the highest ROR for increased motivation to eat, had the lowest ROR among the SUs for the behavioral increase in eating (**Figure 14**). Intra-class heterogeneity in disproportionality was observed in weight increased for DPP4is, SGLT2is (**Figure 15**).

When all the disproportionality calculations are visually tabulated in a heat map in **Table 5**, GLP1RAs appeared to have the most disproportionate signals among ADD classes with more than 1 medication included.

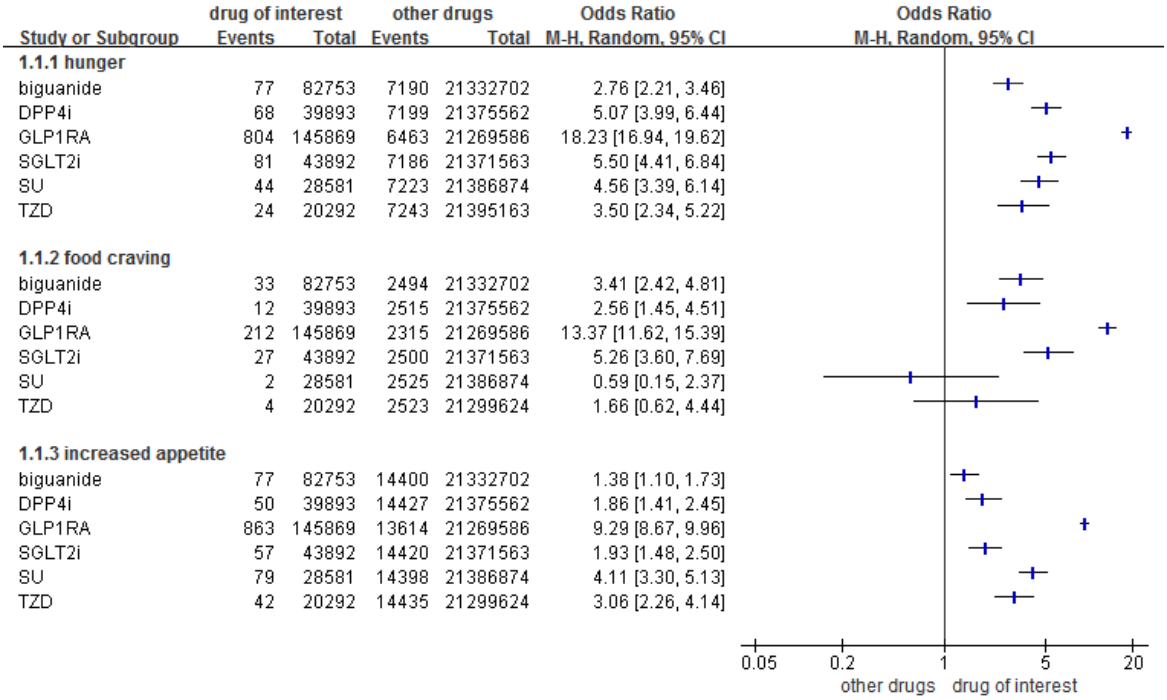

Figure 8. Forest plot presentation of disproportionality of events of increased eating drives ADRs for ADD classes

Hunger was a positive safety signal for all classes of ADDs. *Food craving* was a positive safety signal for metformin, DPP4i, GLP1RAs, SGLT2is. It was not disproportionately reported for SUs. For TZDs, there was a trend toward imbalance in reporting rate, but due to a relatively large confidence interval, did not meet disproportionality definition. *Increased appetite* was a positive safety signal for all classes of ADDs.

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

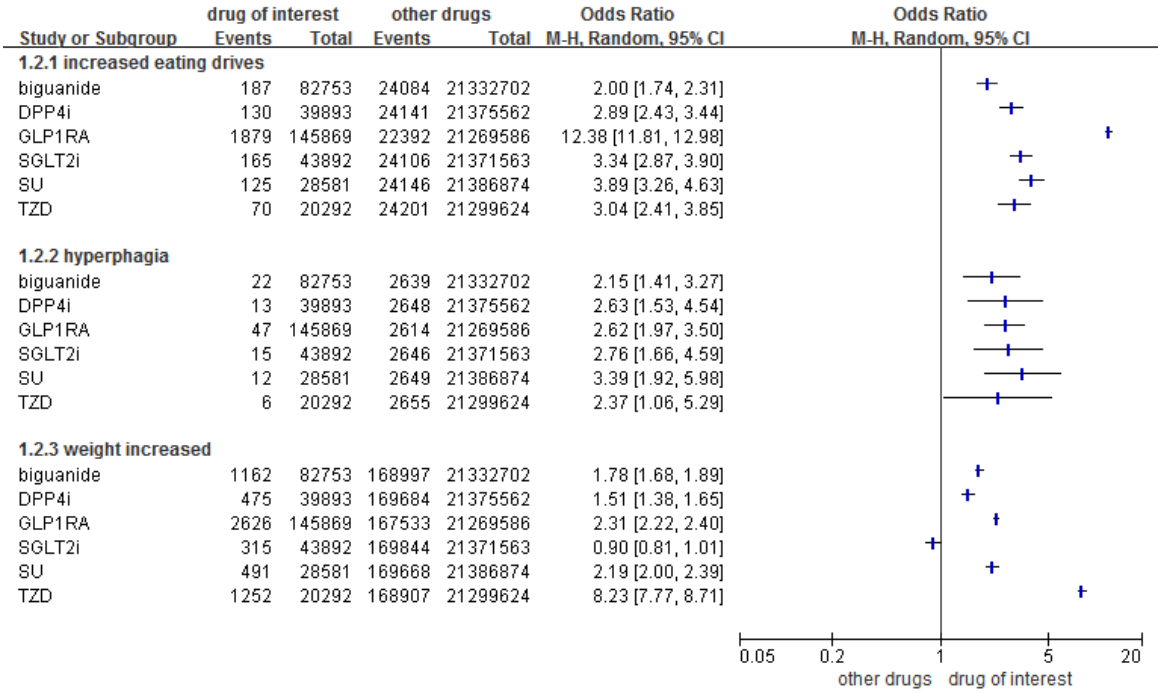

Figure 9. Forest plot presentation of disproportionality of eating related motivation-behavior-physical sign reported as ADRs for ADD classes

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

The aggregate screening query of increased eating drives yielded a positive safety signal for all classes of ADDs. *Hyperphagia* was a positive safety signal for all ADD classes. *Weight increased* was a positive safety signal for all ADD classes with the exception of SGLT2is.There were more total ADR cases for *weight increased* and relatively few cases of *hyperphagia*

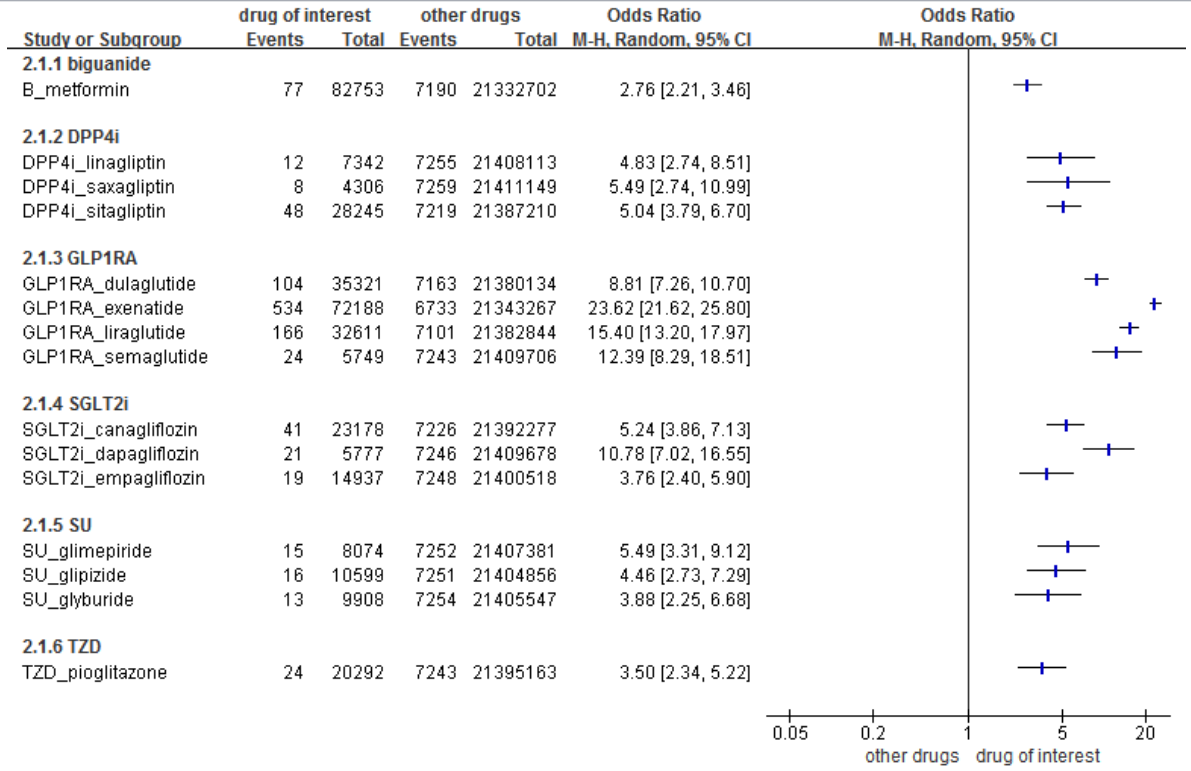

Figure 10. Forest plot presentation of disproportionality of ADR *hunger* for 15 ADD drugs from 6 classes

Hunger was a positive safety signal for all ADDs.

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

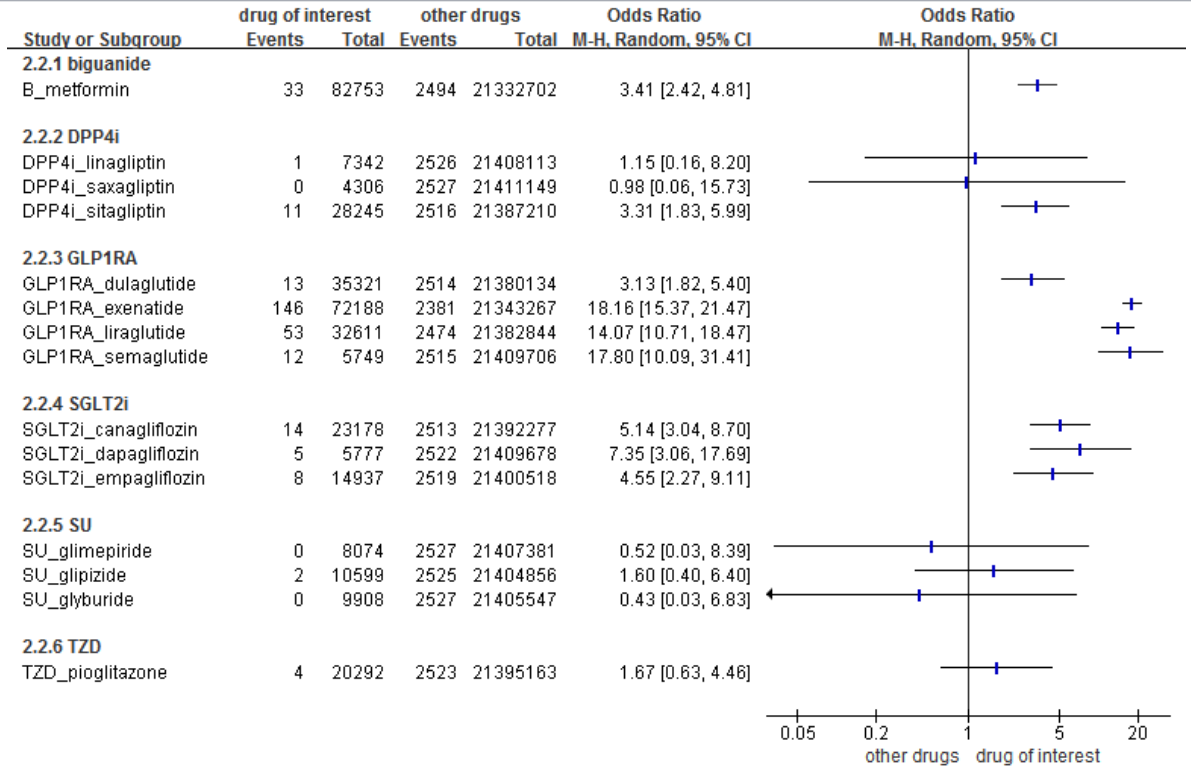

Figure 11. Forest plot presentation of disproportionality of ADR *food craving* for 15 ADD drugs from 6 classes

Food craving was a positive safety signal for metformin, all GLP1RAs and some SGLT2is, DPP4is

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

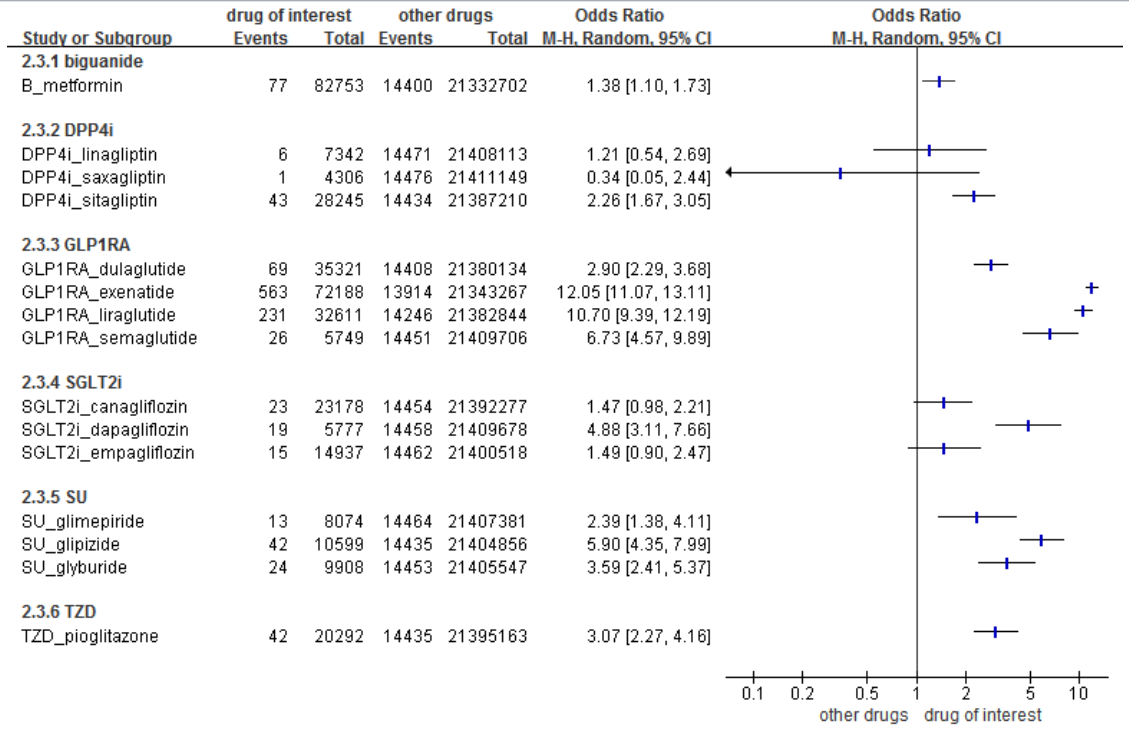

Figure 12. Forest plot presentation of disproportionality of ADR *increased appetite* for 15 ADD drugs from 6 classes

Increased appetite was a positive safety signal for metformin, pioglitazone, all GLP1RAs, SUs, and some SGLT2is, DPP4i

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

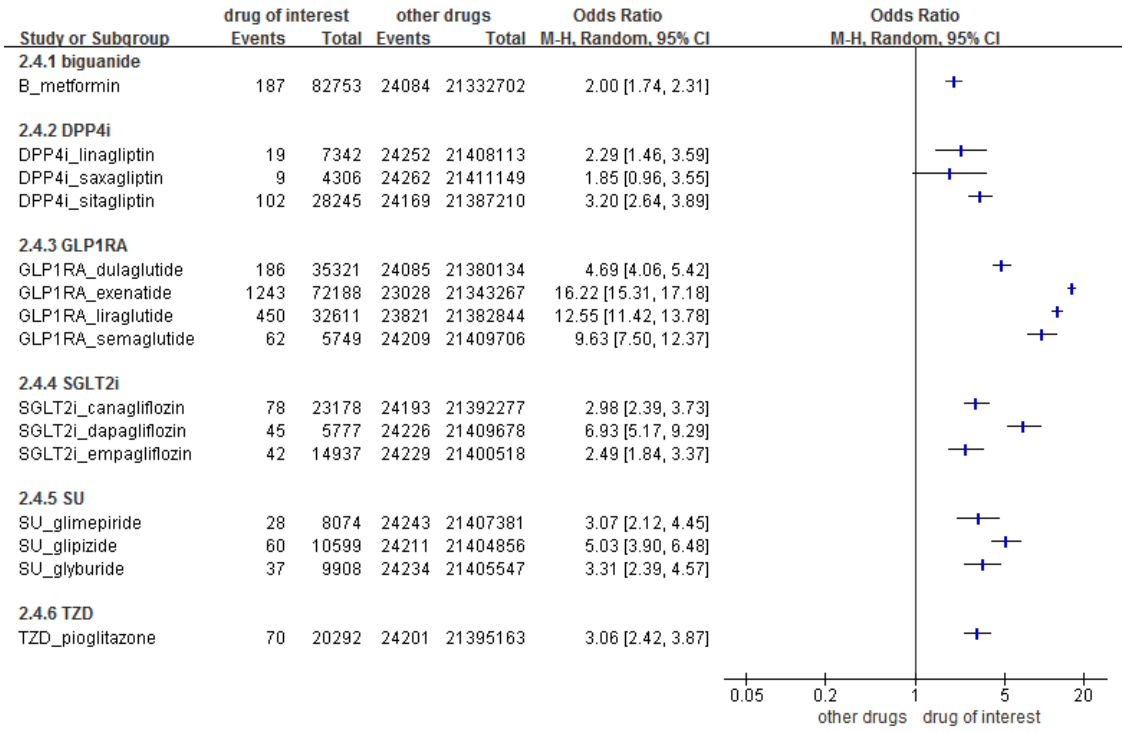

Figure 13. Forest plot presentation of disproportionality of increased eating drive ADR for 15 ADD drugs from 6 classes

The aggregate search for increased eating drives yielded positive safety signals for all of the ADDs except saxagliptin

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

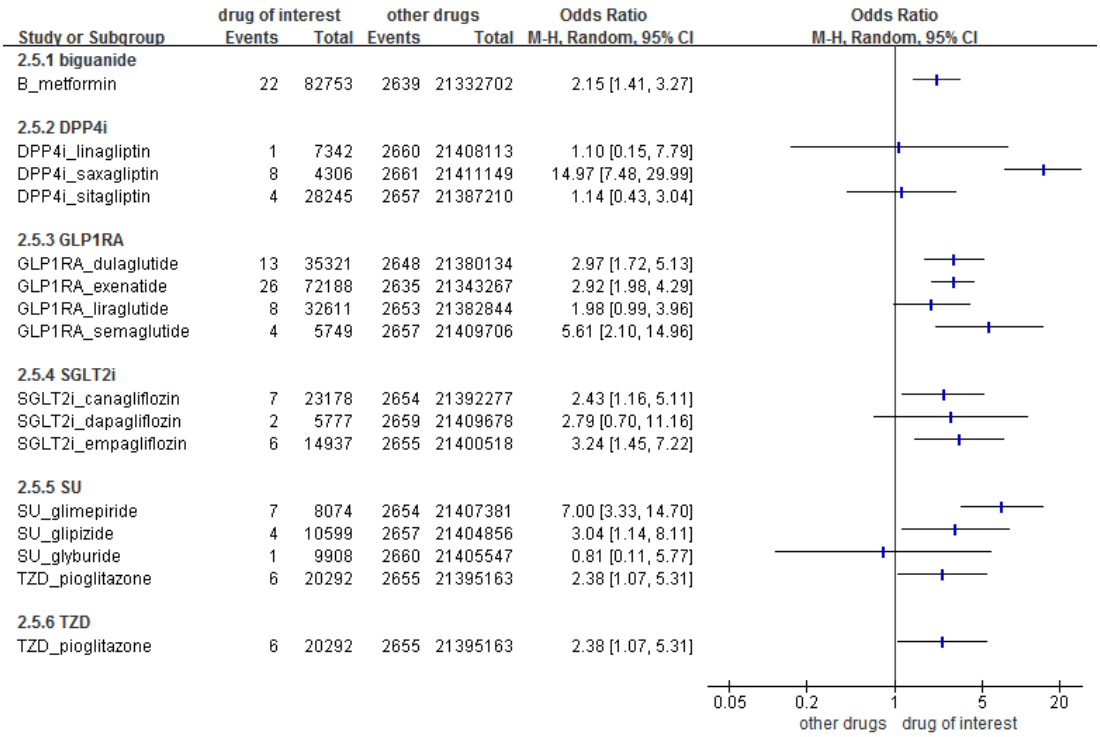

Figure 14. Forest plot presentation of disproportionality of ADR *hyperphagia* for 15 ADD drugs from 6 classes

Hyperphagia was a positive safety signal for metformin, saxagliptin, dulaglutide, exenatide, semaglutide, canagliflozin, empagliflozin, glimepiride, glipizide

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

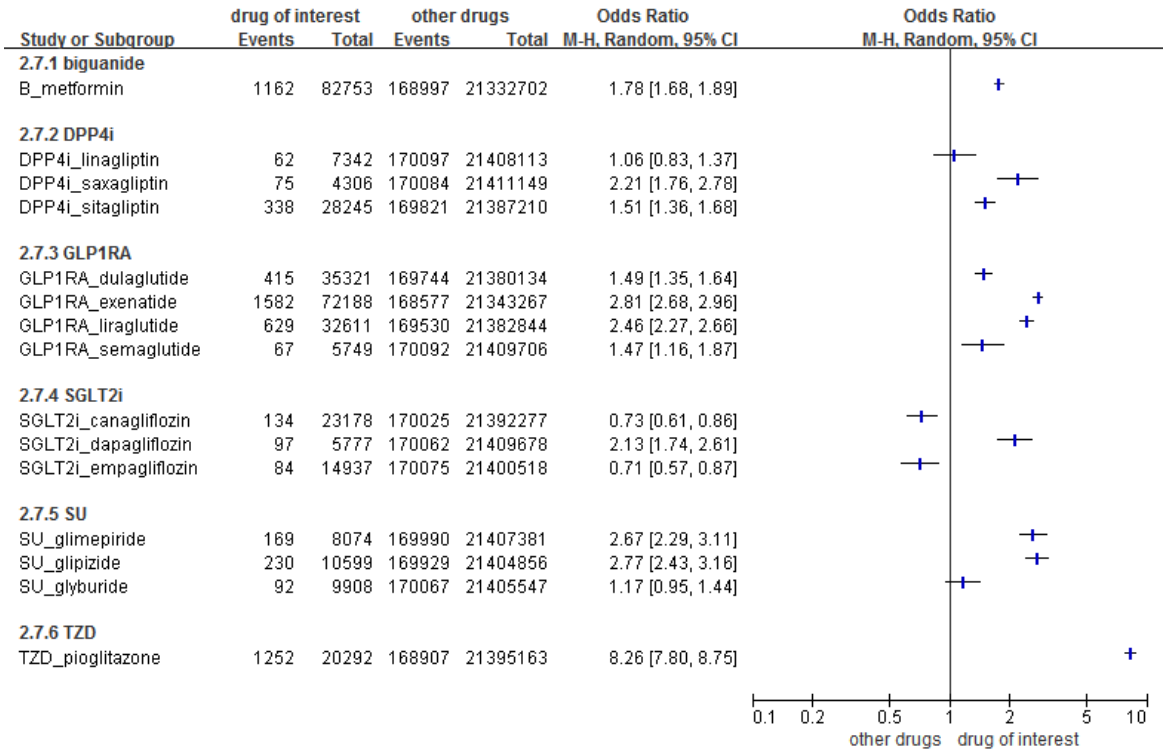

Figure 15. Forest plot presentation of disproportionality of ADR *weight increased* *a* for 15 ADD drugs from 6 classes

Weight increased was a positive safety signal for most ADDs except canagliflozin, empagliflozin, linagliptin and glyburide.

ADR: adverse drug reaction, ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

Table 6. Heat map summary of drug-event pair disproportionality calculations (RORs)

drug class	drug	ADR PTs					
		motivational				behavioral	physical exam
		hunger	food craving	increased appetite	aggregate	hyper-phagia	weight increased
biguanide	metformin	2.76	3.41	1.38	2	2.15	1.78
DPP4i	linagliptin	4.83	1.15	1.21	2.29	1.1	1.06
	saxagliptin	5.49	0.98	0.34	1.85	14.97	2.21
	sitagliptin	5.04	3.31	2.26	3.2	1.14	1.51
GLP1RA	dulaglutide	8.81	3.13	2.9	4.69	2.97	1.49
	exenatide	23.62	18.16	12.05	16.22	2.92	2.81
	liraglutide	15.4	14.07	10.7	12.55	1.98	2.46
	semaglutide	12.39	17.8	6.73	9.63	5.61	1.47
SGLT2i	canagliflozin	5.24	5.14	1.47	2.98	2.43	0.73
	dapagliflozin	10.78	7.35	4.88	6.93	2.79	2.13
	empagliflozin	3.76	4.55	1.49	2.49	3.24	0.71
SU	glimepiride	5.49	0.52	2.39	3.07	7	2.67
	glipizide	4.46	1.6	5.9	5.03	3.04	2.77
	glyburide	3.88	0.43	3.59	3.31	0.81	1.17
TZD	pioglitazone	3.5	1.67	3.07	3.06	2.38	8.26

Positive safety signals (ROR lower margin of the 95% CI >1) are boxed in red, clear negative signals (ROR < 1) are boxed in green and those with ROR > 1, but not meeting disproportional signal definitions are boxed in yellow.

ADR: adverse drug reaction, ROR: reporting odds ratio, CI: confidence interval, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

Class	Drug	Prescription*	Rank†	Share‡	Total share §	Cost ¶	Pocket#	ADD Rank**	ADR rank ††
Biguanide	metformin	83,762,981	4	100	38.3	29.69	4.81	1	1
DPP4i	linagliptin	3,390,521	177	7.4	1.5	653.39	44.74	8	12
	saxagliptin	1,056,369	318	23.8	0.5	590.11	17.72	14	15
	sitagliptin	9,813,528	83	68.8	4.5	737.78	38.34	4	5
GLP1RA	exenatide	1,365,998	285	12.6	0.6	1159.14	33.59	13	2
	liraglutide	4,771,234	143	44.2	2.2	1109.89	54.53	6	4
	dulaglutide	4,223,559	149	39.1	1.9	1144.82	34.4	7	3
	semaglutide	445,540	385	4.1	0.2	1871.83	37.12	15	14
SGLT2i	canagliflozin	3,108,373	191	38.6	1.4	808.06	49.35	9	6
	dapagliflozin	2,304,573	227	32.9	1.1	581.25	36.28	12	13
	empagliflozin	2,649,791	214	28.6	1.2	639.35	52.21	11	8
SU	glimepiride	11,405,689	71	35.9	5.2	25.54	5.73	3	11
	glipizide	17,549,602	44	55.2	8	16.47	5.11	2	9
	glyburide	2,841,093	203	8.9	1.3	22.75	9.74	10	10
TZD	pioglitazone	5,178,776	136	100	2.4	84.43	6.94	5	7

Table 7. U.S. ADD prescription data for 2018 from the Medical Expenditure Panel Survey

ADD: antidiabetic drug, DPP4i: dipeptidyl peptidase-4 inhibitors, GLP1RA: glucagon-like peptide 1 receptor agonists, SGLT2i: sodium-glucose cotransporter 2 inhibitors, SU: sulfonylureas, TZD: thiazolidinedione

* estimated number of prescriptions in the United States in 2018, † prescription frequency rank among all drugs in 2018, ‡ within class prescription share (%)

§ prescription share among antidiabetic medications (%), ¶ annual average total cost of drugs in USD, # average annual patient payment in USD, ** 2018 prescription share rank among the drugs explored in this study, †† total FAERS case report frequency rank among the drugs studied

U.S. ADD prescription data is presented in **Table 6** as a reference. Of note, the drugs with the highest (metformin) and lowest (saxagliptin and semaglutide) prescription frequencies had the highest and lowest number of ISCRs in the FAERS, respectively. Drugs with a higher prescription share but proportionally fewer reporting frequencies were noted, such as glipizide and glyburide. Exenatide, in particular, had one of the smallest prescription shares yet one of the highest frequencies of ADR reports.

4. DISCUSSION

4.1. Summary of key findings

4.1.1. Appearance of a reporting bias of serious and lethal cases in FAERS

Out of a total of 22,002,078 cases reported to the FAERS, the majority of the cases (65%) were reported for serious outcomes, including 9.6% cases of death. A proportional increase was seen in non-serious cases, which made up 23.35% of the reports in 2001–2010 and 38.15% of the reports in 2011–2020.

As shown in **Table 3**, sex distribution and report region distribution stayed relatively stable. The consumer reporting proportion increased numerically from 34.07% of the report to 48.44% from 2001–2010 to 2011–2020. However, missing reporter fields decreased from 16.29% to 1.29%, and it is unknown whether the majority of the missing fields from 2001–2010 were consumers.

In the past decade, HCPs and consumers have almost equally contributed to the database (50.27% of reports from HCPs and 48.44% reports from consumers). The majority of the case reports are from the United States (69.77% in the total database). More cases of ADRs are reported for women than men (54.18% vs. 34.99% in the total database). As demographics are not an element of a valid report, patient age is often missing. In cases where age is available, most of the cases are reported for adults 18–85. Other variables have seen a decrease in missing fields, but not reporting sex has increased

from 7.79% in 2001–2010 to 11.28% in 2011–2020.

4.1.2. Numerous spontaneous ADR reports of increased eating drives were in FAERS

About 0.1% of the total database cases contained reports of increased eating drives. A total of 24,047 cases were reported of increased eating drives, with 14,670, 7,414, and 2,588 cases of increased appetite, hunger, and food craving, respectively. Since 2014, there are more than 1,500 annual case reports of increased eating drives. This data supports the possibility that the FAERS can be used to detect subjective patient experiences as ADRs. In addition, far fewer case reports of increased eating drive and behavior appear in FAERS compared to objective exam findings such as increased weight, which had 170,159 case counts.

4.1.3. Three-fold more reports of increased eating drives are received from consumers (especially women) than healthcare professionals

Consumers reported 2.9 times more cases of increased eating drive ADRs than HCPs (16,672 from consumers, 5,756 from healthcare professionals). For all the ADRs in the database, more cases were reported by HCPs than consumers. The data suggest that increased eating drives are more distressful for the patients than the physicians. Moreover, 2.33 times more cases were received from women (15,583) than men (6,682). Examining all other ADRs, there is an imbalance of sex distribution for increased eating drive ADRs compared to

other ADRs. A greater proportion of reports from consumers and women were also observed for *hyperphagia* and *increased weight*.

In cases where information of the country of report origin was available, 79.5% of the reports came from the United States. This percentage represents 17 times more reports than from the country with the second-highest case numbers (i.e., Canada, with 817 reports). As shown in Figure 5, the out-of-USA proportion for all drugs is higher.

4.1.4. Increased eating drives was a positive ADR signal for all ADD classes; strongest signal was observed with GLP1Ras

For the aggregate signal detection query of increased eating drives which included the PTs *hunger, food craving, increased appetite*, all classes of ADDs yielded positive ADR signals. The strength of the signal was most pronounced in GLP1RAs. Indeed, GLP1RA was the only class that yielded positive signals as a class and for every individual drug in the class through narrow event term search (*hunger, food craving, increased appetite*) as well as broad aggregate term search (increased eating drives).

Of the 28,051 drugs in the database, 1,579 drugs had at least one case report of increased eating drive. The 15 ADDs studied contributed 15.13% of *hunger* cases in the total database, 11.67% of *food craving* and 8.1% of *increased appetite.*

4.1.5. Increased drive to eat, behavioral output, and associated physical exam were not trending together in the FAERS

The ROR values for increased eating drive, *hyperphagia*, and *increased weight* did not trend together. Although comparative analysis is not meaningful using the FAERS data, the value order did not trend together. TZD pioglitazone yielded the highest ROR for *weight increased* but had the lowest ROR for *hyperphagia.* SGLT2i yielded positive signals for increased eating drives and *hyperphagia*, but there was no signal of *increased weight*.

4.2. Interpretations

4.2.1. Bias toward reporting ADRs with serious outcomes

A clinician encounters numerous patient complaints of non-serious ADRs daily. Encounters of serious ADRs requiring hospitalizations, prolongation of hospital stay, lasting disability, or lethal ADR outcomes are rare. Given the observation that the majority of FAERS reports are associated with serious or lethal outcomes, there seems to be a bias toward reporting serious outcomes (**Figure 3 and Table 3**).

Similarly, the majority of ICSRs for ADDs were also serious cases, except GLP1RA, which had the majority of ADRs reported by consumers, which were mostly non-serious. This observation is reviewed later in the discussions

on the observations of GLP1RA reports.

A research of FAERS reporting patterns for statins, biologics, and narrow therapeutics index drugs (NTIs) showed that although under-reporting is seen for all drug groups, there were comparatively higher reporting rates for biologics and NTIs. Since ADDs are probably more like the statins than biologics and NTIs, it is likely that the FAERS data reflect significant under-reporting for ADDs (Alatawi & Hansen, 2017).

An analysis of the UK SRS found that physicians were more likely to report serious ADRs that resulted in hospitalizations, were life-threatening, or caused death compared to healthy patients. The serious cases were much smaller in proportion than the FAERS (32.5% of HCP reports) reports (McLernon et al., 2010).

4.2.2. Patients, especially women, were more likely to report increased eating drives than physicians

Patients and doctors might not have the same treatment priorities in cases of chronic diseases. The discrepancy between patient and doctor goals in management has led to an increased importance of patient-reported outcomes (PROs), including in new drug development. Patients have specific expectations for care, that include discussion of the patient's perspectives about management (Kravitz et al., 1994). These desires are not always

expressed (Bell et al., 2001). When their expectations are not met, patients not only have lower satisfaction with their doctor visits(Bell et al., 2002), but also have less improvement and lower intentions to adhere (Bell et al., 2002).

Analysis of the UK SRS showed that of a total of 41,001 drug-reaction pairs, only 4,340 were reported by both patients and HCPs; 12,226 (30%) were reported by only patients and 24,435 (60%) of drug-ADR pairs were reported by only HCPs. When the patient and HCP reports were analyzed separately, among a total of 16,566 drug-ADR pairs reported by patients (including those also reported by HCPs), 649 pairs (3.9%) were disproportionate signals, 245 (47.8%) of which were reported exclusively by patients and 268 (52.2%) of which were also reported by HCP but were not disproportionate signals (Avery et al., 2011).

Consumer reports to SRSs can be motivated by HCP's indifference to adverse experiences (Arnott et al., 2013; Avery et al., 2011; Härmark et al., 2013). Parents' motivation to submit a spontaneous ADR report included the need to feel their concerns are acknowledged, recognized and recorded. One parent reported, "I felt a bit cross that he[GP] didn't take it [ADR] seriously" (Arnott et al., 2013). Some patients reported their HCPs had not taken their ADRs seriously which motivated them to report; some patients reported the ADR themselves because they didn't think their HCP would report their ADRs accurately (Avery et al., 2011).

In FAERS, there was a proportionally higher reporting of increased eating drives from consumers than HCPs. For all ADD classes, the consumer portion was greater than the HCP portion of reported events of increased eating. And the proportion of women reporting increased eating drives as ADRs were greater than the proportion reporting all ADRs for the same drug. This might be a reflection of greater societal pressure perceived by women on body shape and weight.

4.2.3. What was unexpected—associations of GLP1RA and increased eating drives

4.2.3.1. What was expected of incretin-mimetics

Incretins, such as glucagon-like peptide-1 (GLP-1), secreted from the gut, enhance glucose-dependent insulin secretion and antihyperglycemic actions. Dipeptidyl peptide IV inhibitors (DPP4i) are thought to act by slowing the inactivation of incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP)., thereby increasing insulin synthesis and release from pancreatic beta cells (Drucker, 2005).

Many peptides are involved in the hypothalamic regulation of feeding. Orexigenic peptides include neuropeptide Y (NPY), agouti-related protein (AGRP), melanin-concentrating hormone (MCH), orexin, and galanin. NPY is the key feeding-promoting neuropeptide. Anorexigenic peptides include

alpha-melanocyte-stimulating hormone (a-MSH), cocaine- and amphetamine-regulated transcript (CART), glucagon-like peptides 1 and 2 (GLP-1, GLP-2) and prolactin-releasing peptide (PrlRP).

As GLP-1 is an anorexigen, physiologically, the net neurochemical signal can be hypothesized to be directed toward inhibition of eating. In both animals and humans, the administration of exenatide, a GLP-1 agonist, has been shown to reduce food intake (Amylin Pharmaceuticals, 2009).

DPP4is can have bidirectional effects on feeding signals. DPP-4 inactivates the incretin hormones GLP-1 and GIP. DPP-4 cleaves orexigenic hormones NPY (Bjelke et al., 2006), and the N-terminal Tyrosine-Proline residues from Peptide YY(1-36), producing PYY(3-36). PYY(1-36) stimulates appetite through Y1 and Y5 receptors while PYY(3-36) suppresses appetite ss through Y2 receptors (Ballantyne, 2006). Hence, presumably, a DPP4is can increase both anorexigenic signal GLP-1 and orexigenic signals NPY and PYY. In one study, DPP-4 activity is reduced in both anorexia nervosa and bulimia nervosa, once again suggesting bi-directional effects (Van West et al., 2000). In a study of obese children who participated in a one-year lifestyle intervention program, reduction in DPP-4 levels correlated with reduction of body fat as well as PYY levels (Reinehr et al., 2010). As described in the previous paragraph, the PYY total level is not very informative. In a small study of 12 patients with diabetes treated with sitagliptin, reduced levels of total PYY and

PYY(3- 36), and increased PYY(1- 36) were observed (Aaboe et al., 2010). In the study, however, no change in incretin levels was observed, making interpretations difficult.

An indirect marker of eating may be weight, although many compensatory physiologic mechanisms are influenced by individual constitutional makeup that does not allow for the direct association. In clinical trials with Januvia, a DPP4i, the effect on weight has been variable (Merck & Co., n.d.). In monotherapy of Januvia, body weight did not increase from baseline compared to a small reduction in patients given placebo. In combination with glimepiride with or without metformin, Januvia had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. −0.4 kg). When Januvia was added to insulin with or without metformin, both groups had an adjusted mean increase in body weight of 0.1 kg from baseline at week 24. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo. Compared to glipizide, sitagliptin-treated patients had a greater mean decrease in body weight (−1.5 kg vs +1.1 kg). In combination with pioglitazone, Januvia-treated patients had a greater mean increase in body weight compared to pioglitazone alone (3.0 kg vs. 1.9 kg). The discussions above are summarized in **Tables 8 and 9**, respectively.

Table 8. Summary of neurohormonal changes and effect on feeding signals of GLP-1 agonist vs. DPP-4 inhibitor.

Drug class	Change in neurohormonal signal	Effect on feeding of signal change	Net effect on feeding
GLP-1 agonist	↑GLP-1	anorexigenic	anorexin
DPP-4 inhibitor	↑GLP-1	anorexigenic	?
	↑NPY	Orexigenic	
	↑PYY (1-36)	Orexigenic	

Table 9. Summary of clinical trial observations on food intake and weight of GLP-1 agonist vs. DPP-4 inhibitor.

	Effect on food intake	Effect on body weight
GLP-1 agonist	↓food intake	Weight loss
DPP-4 inhibitor	?	Weight neutral/↑/↓

Clinical trial patients are observed in rather artificial settings where eligibility criteria do not necessarily represent real-world patients. Continuous monitoring of weight and a diabetes-related lifestyle might lead patients to be more cognizant and compliant with prescribed diets and ways of living. Still, given the proposed mode of action of incretin mimetics and its effects on food intake and weight observed in clinical trials, it was expected that GLP1RAs would be associated with less increased eating drives. For DPP4is, it was

expected there would be subgroups of patients who have increased eating drives and other subgroups with decreased appetite.

4.2.3.2. Surprise of GLP1RAs

The disproportionality calculations of DPP4is were unsurprising, but those of GLP1RAs were unexpected. An unmet need of patients with diabetes, especially overweight or obese patients with diabetes, is a drug that not only addresses glycemic control but also leads to substantial weight loss. In this context, the industry, clinical, and patient communities were excited about the development and launch of incretin-based therapies, with GLP1RA inducing weight loss and lowering blood pressure. The launch of Saxenda as an obesity drug flooded the local clinics with obese and non-obese people seeking to lose weight despite high out-of-pocket medication costs and the inconvenience of three self-injections each day. In Korea, Novo Nordisk's supply of Saxenda was unable to keep up with increasing market demand and ran out of stock a few months after launch. Thus, it was a surprise that GLP1RAs had the strongest associations with increased eating drives as ADRs. Potential explanations were considered.

4.2.3.2.1. Some patients developed GLP1 neutralizing antibodies

Of the patients tested after 26 weeks or longer, 8.6% had developed anti-liraglutide antibodies. Additionally, cross-reacting antibodies to native GLP-1 occurred in 6.9% from a 52- week trial and 4.8% from a 26-week trial.

Patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with liraglutide treatment (Novo Nordisk, 2020).

The exenatide prescribing information states that “in a small portion of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control” but does not describe the frequency or magnitude of the neutralizing effect (Amylin Pharmaceuticals, 2009). This may explain the clinical observations of a subgroup of patients who stop responding to GLP1RA. A remaining question is the impact of the antibody cross-reaction with native GLP-1. This could mean that satiety responses are blunted even after discontinuation of the medication.

4.2.3.2.2. GLP1RA, pharmacokinetics, glucodynamic effects

Although all GLP1RAs were disproportionally associated with increased eating drives, the odds were higher for immediate onset agents exenatide and liraglutide. The disproportionality signals were stronger for exenatide (Amylin Pharmaceuticals, 2009), which has a shorter Tmax (2 h) compared to liraglutide (8–12 h). Exenatide is also associated with a shorter terminal half-life (2.4 h) compared to liraglutide (13 h). Steady-state peak-to-trough fluctuations are visibly greater for exenatide compared to liraglutide (Watson et al., 2010). This likely means greater fluctuations in plasma glucose,

which could drive increased hunger at troughs. Alternatively, more rapid decline in glucose may increase hunger based on the glucodynamic theory.

4.2.3.2.3. Reduced food intake and reduced weight cause hunger

The weight-reduced state is characterized by elevated appetite. The biological pressure on appetite can be strong and persistent (MacLean et al., 2017). Calorie restriction will make the liver stimulate its AMP-kinase, which will make new mitochondria, inhibit mTOR and facilitate autophagy, lower insulin, promote weight loss. One other thing happens: leptin level will decline within one day, the brain will immediately sense starvation, and the autonomic nervous system will go into conservation mode, with decreases in body temperature and physical activity, feeling tired and irritable, and painfully hungry (Lustig, 2021).

4.2.3.2.4. Different response patterns to GLP1RA

There cannot be a single magic bullet to reduce food intake in people. Emotions, neuroendocrine signals, cognitive restraint are integrated to produce eating. Both within-meal and between-meal aspects must be affected by medication to yield a net effect of reduced eating. Within a meal, flavor stimuli resulting in hedonic judgment can stimulate eating and impairments in satiety signaling can impair termination of a meal. Between-meal signals will affect long-term influence on meal size and timing (Geary, 2012). In its totality, eating is fundamentally a learned experience as described in the

introduction.

For a drug to have lasting effects on reducing food intake it will need to affect food choice, meal patterns, and snacking (Halford, 2001) rather than change in a single neuropeptide signal that affects satiety. The short-term effect of an appetite-suppressant can depend on immediate changes in the physiologic signals that stimulate eating, but the long-term effect will be influenced by homeostatic systems.

It was first observed in 1975 that alpha-noradrenergic stimulation led to voracious eating. In the years that followed, various behavioral experiments showed that levels of norepinephrine (NE) and responsivity changed during different states of energy homeostasis, environmental stress, and other physical conditions. Decades after the behavioral research, NE's complex interactions with leptin, lipopolysaccharide, interleukins to influence feeding were identified (Halmi & Yum, 2007). The biology of GLP-1 may take many more years to be fully understood, but based on learnings from other neuropeptides, it too is likely to be influenced by energy homeostasis, environmental stress and other physical conditions. Hence, patients may have different responses to a drug that potentiates its signals based on their individual physiology and pathology.

Drug clinical trials report means. Usually, great diversity in the magnitude of

responses to any medication is seen. As an example, a small study of exenatide in adolescent obesity graphically displayed individual trajectories of body mass index, which were highly variable (Kelly et al., 2013)

Many people in the real world have various drug responses from the mean value observed in clinical trials. Furthermore, AEs happen in outliers. If an AE happened in the majority of patients, then the drug's benefit-risk ratio would have been significantly altered and perhaps not authorized for marketing. Therefore, it is always essential for clinicians to keep an open mind about patients reacting, unlike the average.

There may also be user-dependent safety issues in different subgroups based on sex, age, comorbidities, and genetic factors. Based on animal research, GLP-1 agonism to improve β-cell replication was affected by treatment duration, age, and diet composition (Arakawa et al., 2009). Female rats displayed higher sensitivity to the food reward effect of GLP-1 receptor activation (Richard et al., 2016). In normoglycemic people, baseline serum GLP-1 has been shown to be higher in women by 20% compared with men (Tramunt et al., 2020). Higher blood pressure has been shown to be associated with lower GLP-1 response to oral glucose (Lundgren et al., 2019). Variability in clinical response to GLP1RAs may be genetically influenced; in cohorts with homogeneous adherence to diet, exercise and antidiabetic treatment, non-responders to GLP1RAs had specific allelic patterns of GLP-1 receptor

(Karras et al., 2018). Polymorphisms in GLP-1 receptor genes are associated with variation in liraglutide response (Kyriakidou et al., 2021). The influence of genes on GLP-1 receptor activity may be mediated by sex and nutrient consumption (Nishiya et al., 2020).

4.2.3.2.5. Selection bias: patients that are hungrier maybe preferentially prescribed GLP1RAs

The selection of individuals prescribed GLP1RAs over other antidiabetics may explain the signal strength. Medical society guidelines recommend GLP1RAs be prescribed to patients who are overweight, obese and need to control their appetite. Hence, it is likely that patients prescribed this class of ADD are likely to be hungrier, to begin with.

4.2.3.2.6. More consumer reports most of which were non-serious

The distribution of reporter type may also have influenced the disproportionality calculations for GLP1RA. With a greater proportion of consumer-driven reports of non-serious outcomes, there is a greater likelihood of reporting soft signals including patient subjective drug experiences.

As described in Section 3.2, the GLP1RA reports, unlike ICSRs from other ADD classes, had more non-serious reports than serious reports. Whereas 95.2% of TZD ICSRs were serious cases, 72.08% of GLP1RA ICSRs were non-serious.

For the GLP1RA ICSRs, 53.17% of the serious excluding death (20,631) cases were reported by HCPs and 46% (17,850 cases) by consumers. For the non-serious cases, 80.83% (90,218 cases) were reported by consumers and 18.65% (20,819 cases) by HCPs.

As shown in **Table 7**, exenatide is the 13th most prescribed ADD among the 15 in this study with a 0.6% prescription share among the ADDs. Yet, it had the second-largest number of ICSRs in the FAERS, closely following metformin which had 38.3% of ADD prescription share. Given the relatively high annual cost of treatment and high out-of-pocket costs, GLP1RAs may have had more patient assistance programs, which may have led to greater interactions with the manufacturer, leading to more consumer-driven ICSRs.

Since the ROR takes into account the ratio of AE of interest among all AEs reported for the drug, if the drug is associated with a large number of case reports for a particular AE or AE class (such as serious ADRs that have received publicity), then the calculation of risks for other AEs may decrease.

As an example, within TZDs, the numeric frequency of eating-related AEs was higher for rosiglitazone, but disproportionality calculations were higher for pioglitazone. Rosiglitazone was not included in this study because the prescription share for the drug in the U.S. was 0% in 2018. Rosiglitazone,

which is no longer widely used because of the concern over cardiovascular events, was mostly associated with cardiovascular ADRs in the FAERS. Of a total of 95,539 case reports in the database, there were 34,184 reports of myocardial infarction, 9,475 cases of coronary artery disease, 3,384 cases of acute myocardial infarction, 1,632 cases of cardiac arrest, 14,990 cases of cerebrovascular accident, 1,874 cases of transient ischemic attack. The frequency of ICSRs was highest during the years when rosiglitazone withdrawal was being discussed. For pioglitazone, the highest frequency of AEs was associated with bladder cancer: 8,863 (43.68%) of a total of 20,292 case reports.

For the TZD pioglitazone cases extracted, 95.2% of ICSRs were serious cases. The proportion of eating drive and behavior would be lower, yielding a lower ROR. On the other hand, since only 28% of the ICSRs received for GLP1RA were for serious cases, such dilution of ROR would not have occurred

4.2.3.2.7. RCT evidence of eventual loss of anorexigenic effect with GLP1RA

A randomized clinical trial of 113 patients with obesity, prospectively measured appetitive effects of liraglutide. At week 52, none of the following patient experiences separated the liraglutide group from those randomized to intensive behavioral therapy (IBT): hunger, fullness, food preoccupation, craving frequency, liking of meals. The liraglutide group also received IBT. Hunger in the liraglutide-IBT combination group was reduced compared to

IBT at week 4, the difference most pronounced at week 6, but by week 10, hunger started to return in the liraglutide-IBT group and by week 52 the liraglutide-IBT group did not separate from the IBT group in the change in hunger from baseline. Fullness peaked at week 4 in the liraglutide-IBT group, separating statistically from the IBT group, then gradually decreased, no longer separating from the IBT group by week 24, then returning to baseline by week 52. Craving frequency was eventually higher in the liraglutide-IBT group by the end of the follow-up period (Tronieri et al., 2020).

4.2.3.2.8. Betrayal of expectations

Consumer reports to SRSs may be motivated by emotional and psychological reasons (Arnott et al., 2013). With the claim of reduction in hunger and appetite, early satiety and weight reduction, patients prescribed GLP1RAs may have high hopes for results. When these expectations are betrayed, maybe they are more likely to report the lack of efficacy as feeling hungry, increased appetite and food cravings. Patients may not always voice what they want to their physicians and their wants and expectations may be shaped by various sources of information other than their physician (Härmark et al., 2013). SRSs may be a place where patients can voice their concerns or dissatisfaction while preserving their secretive cravings and behaviors.

4.2.4. Discordance in signal directions of eating drives, eating behavior, and

weight increase

To see whether the signals are mutually validating, it is useful to note whether similar constructs are trending together and dissimilar constructs are discriminating against each other. It is impossible to look for discriminant validity as discriminant phenomena in the same individual are not collected. Although the aggregate query term for increased eating drives and its components seemed internally consistent, this is also not evaluable. This trend likely occurred because the 3 PTs are used interchangeably in daily life and coding was consequently distributed among them. To examine the congruence of signal directions for cross-validation, the assumption would be that all phenomena are looked for and recorded.

The discordance in signal direction of eating drives, eating behavior, and weight gain could be due to 3 possibilities: (1) not all ADRs are reported (2) motivational aspects of behavior and behavior itself may not be discriminated during the reporting or coding process, (3) the drives, behaviors, and the metabolic outcome can occur independently. For example, some patients might not eat more despite increased eating drives, others might not gain weight despite eating more, and some subjects gain weight without overeating.

4.2.4.1. Not all ADRs are reported and selection of PT during coding may impact signal detection

To explore whether items of logical relationships are associated, the items

should be available from the same individual. For instance, if one patient was asked about appetite and weight was not measured while another patient did not discuss eating drives or behaviors but only measured weight, the relationship between the variables cannot be assessed. SRSs only contain what is reported without the remaining data.

Furthermore, the selection of PT during the coding process may impact signal detection, which may be particularly true for soft signals. For example, saxagliptin had the fewest cases of a motivational increase in eating drive among the DPP4is but had the highest case numbers of hyperphagia among the DPP4is. Perhaps there was a preferential selection of hyperphagia over motivational event terms during the coding process. It may be for signal detection purposes that the broader aggregate term should combine motivational and behavioral increases in eating.

In a hypothetical (and likely) scenario, a patient's response to a physician's question asking about how his/her sleep and appetite have been (a psychiatrist almost always asks about these) during the past week or so could be:

"Sleep has not been a problem. But I seem to be hungrier and am eating more often. Sometimes I even eat at night before bed and seem to seek desserts like cake, cookies. I have to go grocery shopping more often and am spending more money on food than before. I think it may be due to the new drug

because I'm experiencing this since the medication change. I'm concerned about weight gain."

The physician might do one or more of the following:

1. Record "sleep, appetite good" in the chart. This doctor is only concerned when there is no appetite.
2. Say "that must be difficult" and do nothing. Repeat at next visit. The patient will eventually stop reporting the problem.
3. Acknowledge and discuss strategies to improve diet adherence, for instance, suggesting hydration or distraction strategies such as walking or substituting cake with fruits.
4. Order labs to check for metabolic profiles.
5. Schedule a session with a dietician.
6. Refer the patient to cognitive-behavioral group therapy for overeaters.
7. Prescribe an appetite suppressant.
8. Change the medication.
9. Reduce the dose of the medication.
10. Report the experiences as an ADR.

If the physician were to report the ADR, it could be reported verbatim as per the patient's report, in which case the coding specialist may assign any or some combination of the PTs illustrated below.

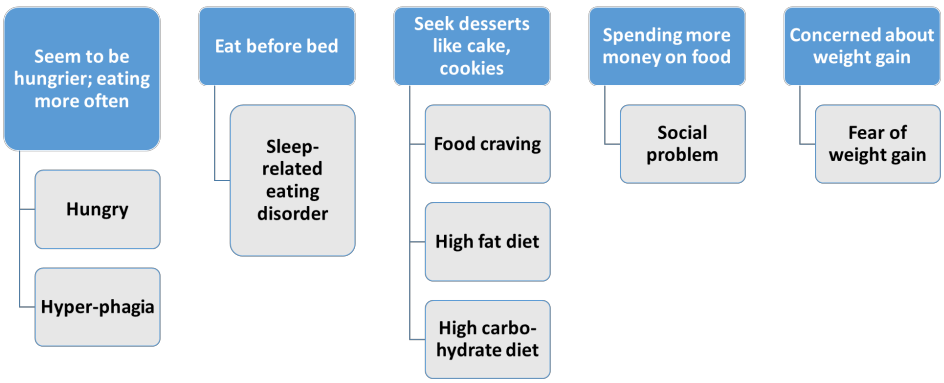

Figure 20. A scenario of verbatim MedDRA preferred term (PT) coding for a patient's report of increased eating drives.

Patient verbatim in solid blue boxes are coded to the corresponding MedDRA PTs below

Other PTs may also be coded such as *diet failure*, *carbohydrate tolerance increased*, *appetite disorder*, *increased appetite*, *diet noncompliance*, or *unhealthy diet*. In the scenario above, there is no exact PT match for night eating. This could simply be coded as *hyperphagia* or a coding specialist may be preoccupied with the diurnal specification and select *sleep-related eating behavior*. Because of such coding errors, soft ADRs should have sufficient cases to evaluate a signal.

Alternatively, the physician might, in concordance with the physical examination data, conclude on one PT: *increased weight*. In the "subjective, objective, assessment, and plan" framework of medicine, physicians are trained to assess the patient's subjective experiences, preferably arriving at one all-encompassing assessment integrating the patient's symptoms and the physician's observations, or another form of reductionistic conclusion (e.g., identifying several additional rule-out conditions). The spontaneous reports to the EudraVigilance showed that patient report PTs were more likely to belong to the general disorders SOC (which includes symptoms such as hunger, and early satiety) in the MedDRA scheme, whereas HCP report PTs were more likely to belong to the Investigations SOC, which include objectively quantifiable markers such as laboratory results, waist circumference, and weight. Also, patients were more likely to report ADRs that affected their quality of life (Banovac et al., 2017).

In reality, coding associates do not code every verbatim phrase, but make an assessment. Moreover, the patient's verbatim statement arrives in part and not in its entirety. Only in the cases of AESIs (AEs of special interest), a pharmaceutical physician might request a full narrative account of the patient experience. A soft subjective signal such as hunger would not qualify as an AESI.

Manufacturers and distributors of medicines, through which most

postmarketing SRSs are channeled, have different levels of staffing. Moreover, the number of coding specialists per product, experience levels of the specialists, risk management systems that advise and oversee the specialists vary. Additionally, the intensity and seriousness with which employees (e.g., sales personnel) are trained to recognize and report ADRs from customer interactions differ. These variations affect the quality of the coding process.

4.3. Limitations

4.3.1. Cannot assess comparative risk based on strength of the signal

FAERS is a non-random sample, that is, patients prescribed one drug over another were likely to have had underlying clinical characteristics that made them suitable for the specific medication. In that case, comparisons of signal strength between drugs are not useful. The detection of safety signals is still of clinical value, however, as it has meaning within the specific populations prescribed each medication, such as antidiabetic drugs.

Analyses of aggregate data from non-random samples, including the mining of big data, cannot consider the delicate and complicated process of clinician decision-making. The clinical characteristics of individual patients would have influenced physicians' selection of a specific class of antidiabetic agent, and furthermore, a specific agent within a medication class.

Still, GLP1RAs can be considered to have produced the strongest signal for increased eating drives not because of the magnitude of disproportionality (i.e., ROR value), but because it had the most disproportionate signals (**Table 6**).

4.3.2. The magnitude of the problem cannot be estimated

The FAERS database is a non-random sample in which no one is intentionally excluded. In theory, it includes everyone who takes any drug. In reality, AEs are under-reported in spontaneous reporting systems.

As discussed in section 1.3.2, attempts to use prescription data to estimate the denominator is no longer frequently used because the reporting rates are influenced by multiple factors other than the true incidence of ADRs.

For example, the estimated number of prescriptions in the United States in 2018 (Kane, 2020) for GLP1RAs is 10,806,331. The total number of ICSRs for these four drugs reported to FAERS in 2018 was 13,997. For DPP4is, there were a total of 10,869,897 estimated prescriptions in the United States. There were a total of 2,667 ICSRs reported to FAERS in 2018 for these 3 drugs. The total number of estimated prescriptions is similar but the number of ICSRs for the given year is more than 5-fold different. This most likely does not mean that patients experience 5-fold more ADRs in one class over the other.

4.3.2.1. Underreporting and reporting bias

Since the knowledge and attitude of health professionals are important determinants of spontaneous reporting (Lopez-Gonzalez et al., 2009), physician and patient expectations of weight gain and effects on eating likely influenced the reporting rate.

ADR reporting is dependent on the reporter's skill and experience to detect the ADR, level of understanding of the SRSs, and their workload (Hazell & Shakir, 2006).

In a survey conducted to assess doctors' attitudes toward reporting of ADRs in the Netherlands, the most frequent reasons for not reporting were: uncertain causality, the ADR being trivial, and the ADR being too well known. Some physicians didn't know the existence of a reporting scheme or how to report (Eland et al., 1999). Other reasons for not reporting included fear of lawsuit, complacency, guilt for having caused damage, insecurity and indifference (Gent & Shigematsu, 1978)

In another study, physicians who actively report ADRs had more knowledge on ADR reporting and were more interested in pharmacotherapy (Passier et al., 2009).

Some of the reasons for reporting included: motivation to contribute to

medical knowledge, reaction previously unknown to the reporter, known reaction, new drug, significant reactions and severity of reaction (Edwards, 1997).

Despite time constraints and busy schedules, education has been shown to increase physician reporting. In an FDA-sponsored project executed by the Rhode Island Department of Health, physician education resulted in a 17-fold increase in reports submitted directly from Rhode Island. Physicians demonstrated significant gains in knowledge and positive attitudes toward SRS, which led to an increase in the number of total reports as well as severe ADR reports. This phenomenon was observed only locally where the project was conducted, and not nationally (Scott et al., 1990).

According to a PV textbook, the FDA's position on reporting rates is that because of substantial underreporting, if the reporting rate is disproportionately higher than background expectations, this may be a strong indicator of a high true incidence rate. On the other hand, the FDA cautioned that a lower than background rate does not mean the drug is not associated with increased risk for that AE (Cobert, 2011).

4.3.3. Association is not causation

Although the reporter's initiation for reporting is likely motivated by

suspicion of causality, the signals explored in this study are disproportionate reporting indicators and should not be understood as causal indicators.

There are views that spontaneous reports are genuine and general clinical concerns about a drug and its suspected reactions and therefore, must be treated as "valid" and called "clinical concerns" rather than "spontaneous reports" (Edwards, 1999). The FDA shares this view and treats all spontaneous reports as adverse reactions.

4.4. Implications

4.4.1. FAERS can be used to detect signals of subjective patient experience ADRs

In line with the FDA trend to incorporate PROs in the drug approval process, subjective patient experiences that are suspected to be ADRs might contribute to enhanced treatment adherence, and thereby effectiveness. Given that 0.1% of the database (24,047 cases) were reports of increased eating drives, there appears to be significant reporting of adverse patient subjective experiences to the FAERS. While traditional PV signal detection has focused on ADRs with serious outcomes, current data suggests a new area of future PV focus on patient drug treatment experiences.

4.4.2. Consumer reports may be more sensitive to detect soft signals of

subjective patient experiences

Immediate and long-term goals of chronic disease management can be different for patients and doctors. What worries doctors and what distresses patients may be different. The different proportion of reporters for the increased eating drives ADR from all ADDs suggests that hunger, increased appetite, and food craving are more of a concern for patients than their physicians. If a drug causes those undesired effects or is suspected to have caused them, it can threaten treatment adherence as well as the therapeutic alliance. Women seem to be more interested in or sensitive to the increased eating drives associated with drug treatment. Given the different interests, goals, and thresholds for aborting treatment, consumer reports may be a more sensitive data pool to mine for signals related to patient subjective distress.

Anderson et al. (2011) researched patient perspectives about ADRs where patients viewed SRS as an opportunity to describe their experiences. Patients valued SRSs' independence from HCPs, whom they regarded at times as being dismissive of their experiences (Anderson et al., 2011).

In an examination of the UK SRS, patient reports were richer in descriptions, including the impact of ADR on patients' lives. The addition of patient reports to HCP reports led to the identification of 47 new serious ADRs (Avery et al., 2011). Another study looking at signal detection using patient reports and HCP reports suggested that they each contribute to the detection of different signals. From the physician reports, the most common disproportionate

signals were from general disorders SOC. In contrast, in the patient dataset, psychiatric disorder signals were most common. The authors recommended analyzing patient and HCP datasets separately as well as together for signal detection (Hazell et al., 2013). From UK and Danish SRSs, clear differences between patient and HCPs were seen in the SOC categories of reports (Inch et al., 2012).

Patient reports enabled the detection of signals such as amenorrhea, pathologic gambling, patchy baldness, dry skin, and subjective experiences such as shock-like paresthesias, change of sense of taste, and thirst (Inácio et al., 2017).

An interesting effort to note and monitor for the future is a patient-centered, web-based platform developed out of Germany (Side Effects.de) that partners with diverse patient advocacy groups. In an analysis of data from April 2019 to September 2020, the majority of patient-reported ADRs were non-serious. Among the few (4.5%) serious ADRs, erectile dysfunction was one of the most frequent (Hasford et al., 2021). This result contrasts with the reporting patterns of physicians where more serious ADRs are more frequently reported (i.e., most physicians would be unlikely to report erectile dysfunction as serious). Therefore, an apparent gap is seen between what is important for patients compared to physicians, the reduction of which should be collaboratively addressed.

4.3.3. Informed consumers may be key to successful PV activities for signals that matter to patients

Manufacturers and distributors holding U.S. market authorization are obligated to report ADRs wherever the company operates globally. Thus, although FAERS is a U.S. database, if the drug is sold outside the United States, then out-of-USA data are also captured. Hence, the FAERs database contains significant numbers of "foreign" case reports.

Based on the reporter characteristics for ADRs of increased eating drives, U.S. patients seem much more likely to report consumer-driven ADRs. As seen with physician surveys, some knowledge of reporting systems and conceptual knowledge of ADRs are probably required for patient self-reporting.

The United States is a country where direct-to-consumer (DTC) drug advertisement is allowed. It is common to see drugs being advertised in magazines and on television. U.S. patients have greater access to drug information and may be more informed consumers. Such informed consumers might be key to capturing signals that distress patients and challenge their treatment adherence.

A UK study by Lorimer et al. (2012) revealed that the majority of patients did not know about the UK SRS, the Yellow Card Scheme, and even when it was

explained to them, patients did not feel it was their responsibility to report ADRs. Moreover, patients felt that they had little or no direct benefit from the reporting scheme (Lorimer et al., 2012). However, for those patients who did report to the UK SRS, 74.8% of submitted reports included a temporal association, and 32.8% used various information sources (e.g., patient leaflets) to confirm associations. This finding suggests that although the proportion of patients who were knowledgeable and willing to report to SRSs may have been few, those patients who do report to SRSs are doing so with a certain level of knowledge on ADR causality (Krska et al., 2011). A study examining the quality of ADR reports assessed by PV specialists using a structured tool, looking at reports of chronology, suspected drug, and patient characteristics, it was concluded that the level and quality of clinical information contained in patient reports were similar to HCP reports (Rolfes et al., 2017).

As of 2014, 44 countries had patient reporting systems and patients contributed about 9% of the total reports: Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Kenya, Latvia, Lithuania, Luxembourg, Malta, Mexico, Morocco, Netherlands, New Zealand, Nigeria, Norway, Peru, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, UK, USA (Margraff & Bertram, 2014). Although not captured in this publication, Korea also has a patient reporting

system through the Korea Institute of Drug Safety & Risk Management (KIDS, n.d.).

Patients in these countries likely have varying degrees of common knowledge about SRSs. A systematic review of patient reports to SRSs found that studies were conducted mostly in the UK, the Netherlands and Australia. Barriers to patient reporting of ADRs included lack of awareness or confusion about reporting systems, difficulties with reporting procedures and lack of feedback on submitted reports. Patients were motivated to prevent others from similar ADRs, seeking feedback, informing health authorities of the ADRS, improving HCP practices, and responding to HCPs not reporting their ADRs. The authors suggested that improving patient awareness with the SRSs, and reporting processes could increase patient reporting of ADRs (Al Dweik et al., 2017).

A qualitative study interviewing national health authorities, pharmaceutical industry associations and supranational organizations in Europe, there were mixed opinions about the value of patient reports. Negative opinions included lack of value, not cost-effective, not helpful in assessing benefit-risk of medicines, and concerns about “a lot of noise.” Positive opinions included capturing different information about what’s important to patients, and what affects patient’s quality of life. One of the interviews provided the opinion that patient reports may not provide “real safety signs” but provide

information on tolerability, adherence, and compliance (Inácio et al., 2018).

4.3.4. Increased eating drives associated with ADDs requires further evaluation

As discussed in previous sections, diabetes itself is prone to increased eating drives. Rapid reduction of plasma glucose or weight or restricted diets may lead to increased experience of hunger, appetite, food cravings. Given the implications for treatment adherence and long-term outcome, the positive signals observed in this study warrant further evaluation.

4.5. Recommendations for signal evaluation of increased eating drives associated with ADDs

4.5.1. For characterization

In signal evaluation, the drug-ADR relationships should be characterized in terms of time-dependence, that is, rapid, with the first dose, early, intermediate, late, or delayed (e.g., target receptor desensitization, neutralizing antibodies). De-challenge and re-challenge information from observing the resolution of the ADR with discontinuation and re-emergence with a re-attempt of drug administration would also be useful information.

4.5.2. Susceptibility factors

Identifying patient characteristics that may be contributing to a user-

dependent ADR, such as age, gender, underlying disease characteristics, and exogenous factors (e.g., sugar consumption, processed food), genetics would be useful. Not everyone will experience a particular ADR: it is always a subgroup, and usually a small subgroup. Identifying the susceptibilities, avoiding or minimizing risks, or identifying risk management strategies would be the ultimate destination of the journey that begins with an identified signal.

5. CONCLUSION

Although there seems to be a bias toward reporting serious and lethal cases in FAERS, the database also contains significant numbers of subjective patient experience ADRs to mine for soft signals. These soft signals might be reported more frequently by consumers than by HCPs. In this context, it seems important that educated and well-informed consumers are necessary for ADR reporting for the PV system to pick up soft signals. Mining consumer reports may be a more sensitive approach to detecting soft signs of patient experiences. Addressing soft signals could have different priorities in the treatment plan of patients and physicians. Understanding the importance of these experiences to the patients will enhance treatment adherence and the therapeutic alliance.

All ADD classes yielded positive safety signals of increased eating drives. Although diabetes itself is associated with this problem, when patients and physicians take the time and effort to report the experience to the system, it should be understood that they had sufficient concern and suspicion about the relationship of their condition to the drug. Given the clinical implications of increased eating drives affecting glycemic control and long-term target organ disease in diabetes, the disproportions of these events in association with ADDs warrant further evaluation.

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국문 초록

임상 개발 과정에서 대부분의 안전성 탐지, 분석 노력은 동물 독성 연구에서 얻은 중요한 결과 또는 1 차 및 2 차 약력학적 효과에 기반한 가설을 사람에서 유심히 관찰하는 것에 집중되어 있다. 약물이 시장에 출시된 후 약물 역학적 연구는 주로 사망률, 심각한 이환율 또는 객관적으로 정량화 할 수 있는 결과들 (예: 검사 수치, 영상 바이오마커)의 분석에 결과에 집중되어 있다. 현존하는 약물 안전의 제도는 임상 현장에서 혹은 실생활에서 환자의 주관적인 약물 경험을 조사하는 데 큰 관심을 보이지 않았다.

이 논문은 기존 약물 감시 데이터베이스 중 미국 FDA의 약물 부작용 보고 시스템 (FAERS)의 빅데이터가 환자의 주관적 약물 경험을 탐색할 수 있는지를 보고자 했다. 환자의 주관적 경험 중 배고픔, 식욕, 음식에 대한 갈망 등 식이 행동의 동기와 연관된 지각들이 약물 부작용으로 경험되고 보고되는지를 탐색했다.

탐색에는 미국 FDA의 시판 후 약물 부작용 데이터베이스에 보고된 당뇨약과 연관된 식사 동기를 증가시키는 부작용이 사용되었다. 미국의

약물 처방 자료를 참고하여 미국에서 많이 쓰이는 6개의 약물군에 속한 15개의 당뇨약과 식욕 증가와 관련된 부작용 용어가 조합된 보고를 추출했다. 부작용 용어로 배고픔 (hunger), 음식에 대한 갈망 (food craving), 식욕 증가 (increased appetite)가 사용되었다. 이 부작용 들은 개별적 신호 탐색에도 쓰였고 세 부작용 용어의 보고 빈도의 합으로도 탐색 되었다. 미 FDA 데이터베이스에서 1968년부터 2020년 12월 30일까지 전체 데이터에서 약물-부작용 조합을 추출하였다. 부작용 신호 탐색에 흔히 쓰는 기법 중 reporting odds ratio (ROR)을 사용하였다. 이는 다른 모든 약과 비교해서 특정 약물의 특정 부작용 보고 비율의 비교의 균형을 보는 불균형 계산 (disproportionality) 방법 중 하나로 이 값의 95% 신뢰 구간의 하부경계값이 1을 넘으면 부작용 신호로 해석했다.

모든 계열의 당뇨약이 식사 동기 증가 부작용과 2.00 [1.74, 2.31]에서 12.38 [11.81, 12.98] 범위의 ROR [95 % CI] 값의 유의한 연관을 보였다. 개별 당뇨약의 식사 동기 증가 부작용의 ROR [95 % CI]은 다음과 같았다: 메트포르민은 2.00 [1.74, 2.31], 리나글립틴은 2.29 [1.46, 3.59], 삭사글립틴 1.85 [0.96, 3.55], 시타글립틴 3.20 [2.64, 3.89], 둘라글루타이드 4.69 [4.06, 5.42], 엑세나타이드 16.22 [15.31, 17.18], 리라글루타이드

12.55 [11.42, 13.78], 세마글루타이드 9.63 [7.50, 12.37], 카나글리플로진 2.98 [2.39, 3.73], 다파글리플로진 6.93 [5.17, 9.29], 엠파글리플로진 2.49 [1.84, 3.37], 글리메피리드 3.07 [2.12, 4.45], 글리피지드 5.03 [3.90, 6.48], 글리부라이드 3.31 [2.39, 4.57], 피오글리타존 3.06 [2.42, 3.87].

FAERS에는 상당한 수의 주관적인 환자 경험 ADR이 포함되었다. 20,000 개가 넘는 부작용 용어 중 세 개의 식사 동기 증가 용어가 전체 부작용 보고 사례의 0.1 %를 차지했다. 약물 주관적 경험은 의료인보다 소비자가 더 자주 보고하는 것으로 보인다. 식사 동기 증가 부작용의 보고자 중 69.33 %는 소비자, 23.94 %는 의료인이었다. 모든 계열의 당뇨약에서 의료인 (9.89-35.48 %)보다 소비자 (33.82-89.70 %)가 더 많은 보고를 하였고, 남성 (25.64-34.36 %)보다 여성 (57.26-72.45 %)에서 더 많은 식사 동기 증가가 보고되었다.

FAERS는 환자의 주관적 경험에 대한 초기 신호 탐색 및 가설 생성을 위한 유용한 도구로 보여진다. 심각한 부작용이 더 선택적으로 보고되는 것으로 보여지나 환자의 주관적 불편함도 충분한 사례가 보고되어 있다. 환자의 주관적인 약물 경험은 의료인보다는 환자가 보고하는 경우가

많았는데 이것이 환자와 의사가 생각하는 치료의 목표와 그 과정에서 중요하게 생각하는 점의 불일치에서 기인하는지를 이해하는 것은 치료의 관계 및 약물 순응도에 중요할 것으로 보여진다. 약물감시체계가 이런 주관적인 환자 경험을 탐색할 수 있는 유용한 도구가 되기 위해서는 약물과 부작용 관리 시스템에 대한 환자의 지식과 이해를 필요로 한다. 미국 FDA 데이터베이스는 의미 있는 정보원이 될 수 있을 것으로 보인다.

주요어 : 배고픔, 식욕, 주관적 약물 경험, 당뇨약, 약물 역학, 시판 후 약물 감시, FAERS

학 번 : 2014-30913