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Methodological guidance for the use of real-world data to measure exposure and utilization patterns of osteoporosis medications

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ABSTRACT

Observational studies of osteoporosis medications can provide critical real-world evidence (RWE) that fills knowledge gaps left by clinical trials. However, careful consideration of study design is needed to yield reliable estimates of association. In particular, obtaining valid measurements of exposure to osteoporosis medications from real-world data (RWD) sources is complicated due to different medication classes, formulations, and routes of administration, each with different pharmacology. Extended half-lives of bisphosphonates and extended dosing of denosumab and zoledronic acid require particular attention. In addition, prescribing patterns and medication taking behavior often result in gaps in therapy, switching, and concomitant use of osteoporosis therapies. In this review, we present important considerations and provide specialized guidance for measuring osteoporosis drug exposures in RWD. First, we compare different sources of RWD used for osteoporosis drug studies and provide guidance on identifying osteoporosis medication use in these data sources. Next, we provide an overview of osteoporosis pharmacology and how it can influence decisions on exposure measurement within RWD. Finally, we present considerations for the measurement of osteoporosis medication exposure, adherence, switching, long-term exposures, and drug holidays using RWD. Ultimately, a thorough understanding of the differences in RWD sources and the pharmacology of osteoporosis medications is essential to obtain valid estimates of the relationship between osteoporosis medications and outcomes, such as fractures, but also to improve the critical appraisal of published studies.

1. Introduction

1.1. Burden of osteoporosis and available pharmacotherapies

Osteoporosis is a disease of low bone mass that results from an imbalance in bone remodeling wherein the amount of bone formed by osteoblasts is lesser than the amount removed by osteoclasts (*Am. J. Med.*, 1991). Osteoporosis greatly increases the risk of fractures that can cause pain, loss of independence, disability, and death (Morin et al., 2011; Ioannidis et al., 2009; Nikitovic et al., 2013; Wiktorowicz et al., 2001). Collectively, osteoporosis affects over 75 million people in the US, Europe, and Japan alone (Kanis JA on behalf of the World Health Organization Scientific Group, 2007). One in three women and one in five men worldwide will have an osteoporotic fracture in their lifetime (Kanis JA on behalf of the World Health Organization Scientific Group, 2007).

Oral bisphosphonates (e.g., alendronate, risedronate) are the most commonly prescribed treatments for osteoporosis and are recommended

Abbreviations: CPRD, Clinical Practice Research Datalink; BMD, Bone mineral density; EMR, Electronic medical record; FIT, Fracture Intervention Trial; GIOP, Glucocorticoid-induced osteoporosis; GP, General practitioner; HRT, Hormone replacement therapy; IMRD, IQVIA Medical Research Database; MPR, Medication possession ratio; PDC, Proportion of days covered; PTH, Parathyroid hormone; RANKL, Receptor activator of nuclear factor kappa-B ligand; RCT, Randomized clinical trial; RWD, Real-world data; RWE, Real-world evidence; SERM, Selective estrogen receptor modulator; SIDIAP, Information System for Research in Primary Care; THIN, The Health Improvement Network.

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as first-line therapy in many jurisdictions (Brown et al., 2002; Eastell et al., 2019; The National Osteoporosis Guideline Group (NOGG) et al., 2017). Other approved therapies include intravenous bisphosphonates (i.e., zoledronic acid, ibandronate), denosumab, raloxifene, and anabolic therapies (e.g., teriparatide, romosozumab). Nasal calcitonin is another therapy for osteoporosis that is no longer marketed in some jurisdictions due to a potential increased risk of cancer (Srinivasan et al., 2020). Clinical trials (Cummings et al., 2009; Black et al., 2007) and meta-analyses (Wells et al., 2008a; Wells et al., 2008b; Amiche et al., 2016; Fink et al., 2019) have shown all of these drugs to be effective in the prevention of osteoporotic fractures, with varying degrees of protection for nonvertebral and vertebral fractures.

1.2. Role of real-world evidence in osteoporosis research

Many clinical questions remain about osteoporosis drug therapy, particularly the effects of long-term osteoporosis treatment, drug holidays, sequential therapy (e.g., switching from a bisphosphonate to denosumab), concomitant therapy (e.g., raloxifene with a bisphosphonate) and treatment in understudied populations (e.g., men, long-term care residents). Randomized clinical trials (RCTs) addressing these questions are infeasible due to the long follow-up periods and very large sample sizes needed to provide meaningful evidence on clinically relevant outcomes like fractures. Further, evidence from RCTs has limited generalizability to real-world patients who would not meet the criteria for trial inclusion – for example, males, patients with multimorbidity or polypharmacy, long-term care residents, and other persons that are not represented in RCTs. A previous study identified that roughly half of real-life alendronate users had at least one clinical characteristic that would have excluded them from the Fracture Intervention Trial (FIT) (Reyes et al., 2016). Although osteoporosis is a disease of aging, the most common exclusion criteria present within the real-world patient population was age, with the FIT trial excluding those over the age of 80 (Black et al., 1996). However, this population represents between 16 % and 25 % of real-world patients (Black et al., 1996). Moreover, in some jurisdictions, up to 33 % of real-world oral bisphosphonate initiators are male (Hayes et al., 2019), but males were excluded from the FIT trial (Black et al., 2006).

Real-world data (RWD), used to derive real-world evidence (RWE), are critical to answer the knowledge gaps on the effects of osteoporosis therapy that are left by RCTs (Wang et al., 2019). Collectively, RWD sources are those that pertain to the day-to-day care of patients and contain information that relates to the status or delivery of healthcare services to patients. RWD typically arise from routinely collected sources such as electronic medical/health records, healthcare insurance databases (e.g., healthcare administrative data), clinical and disease registries, pharmacovigilance and adverse event databases, and prospective cohorts (Strom et al., 2020a).

While observational and retrospective in nature, RWD can be powerful sources of information that can complement RCTs to help guide clinical and regulatory decision making on the optimal use of osteoporosis medications. For example, the extensions of the clinical trials for alendronate and zoledronic acid and meta-analyses of observational studies showed that stopping bisphosphonate therapy after 3–5 years of treatment – otherwise known as a “drug holiday” – is generally safe for most patients due to the long half-life and cumulative deposit of bisphosphonates in bone (Black et al., 2006; Black et al., 2012; Nayak and Greenspan, 2019). Thereafter, observational evidence has demonstrated that extended bisphosphonate exposure is associated with rare side effects like atypical femoral fractures and osteonecrosis of the jaw (Fink et al., 2019; Khan et al., 2015; Shane et al., 2014), and more recent evidence suggests that risk of atypical fractures decrease within 1–2 years of stopping therapy (Black et al., 2020). This complementary evidence from trial extensions and observational studies has led to clinical recommendations and continued implementation of drug holidays after a baseline period of 3 to 5 years of bisphosphonate therapy for many patients not at high fracture risk (Eastell et al., 2019; Adler et al., 2016).

However, RWD are limited to patient encounters with the healthcare system and are thus often missing clinical detail, and exposure data are based on imperfect dispensing or prescribing data. Consequently, it is possible that a patient's exposure status can be misclassified, leading to biased estimates in observational studies. In particular, measurement of osteoporosis medication exposures and treatment patterns in RWD can be challenging due to different medication classes, formulations, and routes of administration, each with different pharmacology, and other complex measurement issues such as adherence. As conclusions from RWE are contingent on the validity of exposure measurement (Acton et al., 2023), high attention to detail in the design, measurement, and analysis is required when using RWD. Nevertheless, despite the importance of accurate exposure measurement in observational drug studies, detailed guidance on the measurement of osteoporosis drug exposures in RWD is limited.

1.3. Rationale and overview

In this review, we present an overview of the important considerations for accurate exposure measurement and provide specialized guidance for estimating osteoporosis drug exposures using RWD. First, we compare two major sources of RWD used for osteoporosis drug studies and provide considerations for osteoporosis medication exposure measurements in each source. Next, we introduce the unique pharmacology of different osteoporosis medications and outline how this pharmacology influences exposure measurement in RWD. We then present considerations for the measurement of osteoporosis medication adherence, switching, long-term exposures, and drug holidays using RWD.

2. Overview of common secondary data sources used in osteoporosis RWE

A key consideration when using RWD is that almost all data sources are typically derived from routine clinical practice, and, therefore, collected for purposes other than research. As a result, the databases often do not contain all variables needed for every research question, have frequent missingness, and have measures that are provided in unequally spaced intervals (i.e., only include patient encounters with the healthcare system). Thus, it is critical that researchers understand the nature of the database available and the underlying healthcare system when conducting observational studies with RWD. Most databases include information on patient demographics (e.g., age, sex, vital statistics, geography, and sometimes race and ethnicity), diagnosis codes from primary care and hospitalizations, and prescription medications. However, there are key distinctions between databases, particularly regarding how medication exposures are captured, and the inclusion of clinical diagnostic information (e.g., imaging data, laboratory results, and cause of death statistics). In this review, we focus on the measurement of osteoporosis drug exposures in two of the main electronic healthcare data sources used to generate RWE: administrative (insurance claims) data and electronic medical records (EMR) (Strom et al., 2020a). However, we acknowledge that this dichotomous classification does not capture the intricacies of different databases within these classifications, nor does it cover all types of available RWD or considerations when these types of data are linked.

Administrative claims databases derived from insurance data or federally funded healthcare systems are one of the most frequently used, and often the largest, databases in RWE. These databases get their name from the fact the data are collected for the purposes of tracking and reimbursing payments for services rendered within the healthcare system (e.g., insurance claims) (Cadarette and Wong, 2015). These data can be generated by individual or aggregated healthcare payer data (e.g., MarketScan data (IBM Watson Health, 2018) or Medicare and Medicaid data (Mues et al., 2017)) or centralized in regions with a single payer

healthcare system (e.g., the Danish National Healthcare registers (Schmidt et al., 2015), the National Health Insurance Database in Taiwan (Lin et al., 2018), Canadian provincial healthcare databases such as Ontario data housed at ICES (Schull et al., 2020)).

Typically, claims-based databases are restricted to information that is essential for reimbursement of services rendered. Thus, for prescription data, the date of pharmacy dispensing, the specific medication dispensed, the quantity dispensed, and the estimated days supply, are typically well-captured. However, information on the indication for use, medications paid for out-of-pocket by the patient, and over-the-counter medication use is not captured in most administrative claims databases (Strom et al., 2020b). Moreover, osteoporosis medications administered by a clinician may be captured via different types of claims with varying levels of detail on dosage than medications dispensed at a pharmacy (e.g., alendronate tablets captured through US Medicare Part D prescription dispensing claims versus zoledronic acid infusions billed through US Medicare Part B outpatient claims) (Centers for Medicare and Medicaid Services, 2021), making comprehensive capture of all osteoporosis medication exposures challenging in some RWD sources (Curtis et al., 2012).

An alternative to claims data is EMR databases that are based on electronic patient records. Among the most commonly used EMR databases are the UK Clinical Practice Research Datalink (CPRD; both the gold and Aurum versions) (Herrett et al., 2015), the National Institutes of Health All of Us Research Program (All of Us Research Program Investigators et al., 2019), the IQVIA Medical Research Database (IMRD) (Myland et al., 2021) that incorporates data from The Health Improvement Network (THIN) in the UK (Lewis et al., 2007), and the Information System for Research in Primary Care (SIDIAP) database in Catalonia, Spain (Recalde et al., 2022). These databases are most commonly derived from documentation created in clinical practice, and therefore, contain details relevant to patient care rather than reimbursement (Strom et al., 2020c). EMR databases have the advantage that they may contain information on imaging or laboratory findings (i.e., bone mineral density [BMD], blood levels of vitamin D) that are pertinent to patient care. Additionally, the prescribed dosing instructions of medications and lifestyle factors (e.g., cigarette smoking, height, weight, and alcohol consumption) are often included within EMR databases.

However, there are some limitations with EMR data that differ from claims-based databases, particularly related to the capture of medications. For example, while a claims database provides information on the date a patient filled a prescription at the pharmacy, EMR data only documents when a patient receives a prescription from the physician (Strom et al., 2020c). This is an important distinction when considering exposure classification, as previous studies have shown that up to 30 % of prescriptions go unfilled by patients (Peterson et al., 2003; Cheen et al., 2019; Kennedy et al., 2020). Thus, the risk of exposure misclassification (i.e., assuming a patient is exposed to a medication when they are not) may be higher in an EMR database than a claims database when studying medications for chronic and asymptomatic conditions, like osteoporosis. Additionally, nearly all EMR data have the same limitation as claims databases regarding missing data on over-the-counter medications (Strom et al., 2020a). Finally, while some care from providers using different EMR systems (e.g., specialist care within another healthcare system) and inpatient hospitalizations may be added by the primary care physician to the patient record, this information is not always complete. Thus, for medications given by providers (e.g., zoledronic acid, denosumab, methotrexate) with separate EMR systems, drug exposure information may be incomplete (Strom et al., 2020c). For example, within the UK, denosumab must be initiated by specialist. Therefore, within the UK primary care practitioner databases, the initial exposure to denosumab will be missing, thereby making an accurate assessment of the treatment start date challenging.

Table 1 provides a high-level overview of the key differences pertaining to the classification of medication exposures between administrative claims and EMR databases. However, not all claims or EMR databases are built equally, therefore, we re-emphasize the importance of transparency in reporting about the database in scientific publications. While administrative claims databases and EMR databases are the most common databases within observational research, there are a number of databases that incorporate both billing and clinical data. For example, US Veteran's Affairs data (Maynard and Chapko, 2004), the Kaiser Permanente Research Bank (https://researchbank.kaiserpermanente.org/our-research/for-researchers/, 2023), and PHARMO data in the Netherlands (Kuiper et al., 2020) have aspects of both claims and

Table 1
Comparison of healthcare administrative (prescription claims) data vs. electronic medical record (EMR) data for osteoporosis medication exposure measurements.

Measurement consideration	Healthcare claims data	Electronic medical record (EMR) data
Purpose of data collection	Reimbursement for medications dispensed or healthcare services rendered	Tracking patient care
Medication capture		
Data generation	Claim is submitted when the medication is dispensed in the pharmacy	Prescription order by the physician noted in the patient record at the date of visit
Initiation of therapy (initial adherence)	Measured - Claims indicate a medication has been dispensed and the quantity is auditable (and therefore highly valid) - Not able to measure if a patient actually takes the medication once medication is dispensed - May consider second claim to ensure true initiation - but caution to avoid immortal time bias (Suissa, 2008)	Not measured - Prescription note indicates the prescription was made, but unknown if the patient filled the prescription at the pharmacy or took the medication. - Important to understand how frequently prescriptions go unfilled in the country/region of the database.
Secondary (post-initial) adherence: persistence, discontinuation, gaps in medication use, and implementation[a] (proportion of days covered/medication possession ratio) of therapy	Measured - Can assess degree of adherence to therapy using dispensing information (drug, strength, date, quantity dispensed, and sometimes days supplied)	Crudely measured - Can be measured based on repeat prescription records - Physician notes on dosing instructions available, but not always complete
Indication	Does not measure, yet can often infer indication for osteoporosis based on dosage strength (Burden et al., 2013)	Usually measured
Directions for use	Does not measure	Usually measured - but with missingness
Over-the-counter medication use and medications paid for "out-of-pocket" (not through an insurance provider)	Does not measure	Does not measure unless noted in free text notes by the physician
Medications prescribed by specialists	Measured	Not measured if EMR is separate - only captured during continued care with common EMR.
Medications given in hospital	Not measured or rarely measured	Not measured
Medications given in long-term care	Depends on jurisdiction	Usually not measured

[a] Preferred term over compliance (Cadarette and Burden, 2010).

EMR databases (e.g., pharmacy claims data and diagnostic/procedural billing codes with laboratory results). Moreover, in many countries it is becoming possible to link across different sources of data to generate a more comprehensive overview of a patient's healthcare trajectory. Many Nordic countries with a universal healthcare system have extensively linked healthcare databases that can combine the claims-based data registers for reimbursement with other clinical or public datasets. For example, linking data from the Danish biologic register with the National healthcare registries, we were able to evaluate the association between expensive biologic medications in rheumatology (i.e., tumor necrosis alpha inhibitors that are not captured in the National prescription register) and bone fractures, adjusting for markers of inflammation and disease severity (Abtahi et al., 2022).

The ability to link between datasets is essential for certain research questions where multimodal data (i.e., diagnostic codes, prescription data, disease markers, and imaging data) are needed. More extensively linked or comprehensive databases can significantly improve the capture of exposures, confounders, and outcomes. Thus, while data linkage requires careful attention to ensure the validity and security of the data (Pratt et al., 2020), it is an important step for advancing clinical research in osteoporosis management.

3. Pharmacology of osteoporosis medications

3.1. Overview of osteoporosis drug pharmacology and considerations for exposure measurement

Given the diverse range of medication classes used to treat osteoporosis, a basic understanding of pharmacology of osteoporosis drugs is important to inform appropriate exposure measurement methods in studies leveraging RWD. Here, we provide a very brief introduction into the general pharmacology of the most commonly prescribed osteoporosis medications: bisphosphonates, denosumab, and anabolic therapies. For each, we describe an overview of the mechanism of action, relevant pharmacokinetics, and intraclass differences that may influence accurate measurement of exposures in RWD. We then briefly cover other less common treatments.

3.1.1. Bisphosphonates

Bisphosphonates are antiresorptive therapies that reduce bone turnover by inducing the death of osteoclasts, primarily via inhibition of farnesyl pyrophosphate synthase (Russell et al., 2008). By restoring partial balance in the bone turnover cycle, bisphosphonates reduce fracture risk by increasing BMD. Zoledronic acid may further reduce fracture risk by increasing muscle strength and thereby preventing falls that can lead to fractures (Huang et al., 2021). Alendronate, risedronate, and zoledronic acid are proven to reduce vertebral and nonvertebral fracture risk in post-menopausal women and women and men with glucocorticoid-induced osteoporosis (Wells et al., 2008a; Wells et al., 2008b; Amiche et al., 2016; Fink et al., 2019; Amiche et al., 2018).

Bisphosphonates are available in oral (e.g., alendronate, etidronate, ibandronate, risedronate, and minodronate) and intravenous (IV; e.g., zoledronic acid, ibandronate) formulations. Oral bisphosphonates are generally first-line drug therapy for osteoporosis and thus are the most common osteoporosis medications worldwide (Eastell et al., 2019; Papaioannou et al., 2010). Alendronate and risedronate are among the most frequently prescribed oral bisphosphonates (Hayes et al., 2019; Curtis et al., 2020). Minodronate, a third generation bisphosphonate, is also commonly prescribed in Japan (Ohishi and Matsuyama, 2018; Liu et al., 2020). Oral bisphosphonates have three dosing regimen options: daily, weekly, and monthly. Zoledronic acid is generally infused every 365 days; however, in practice clinicians may choose to administer it less frequently (e.g., every 18 months) (Reid et al., 2018). Of note, IV bisphosphonates are administered by infusion within a clinic and capture of these exposures in healthcare administrative data may vary by jurisdiction. For example, in Ontario, Canada, zoledronic acid therapy is processed as a pharmacy claim (Cadarette et al., 2012), yet for U.S. Medicare beneficiaries, zoledronic acid therapy may be billed either through Medicare Part D (pharmacy) claims or Part B (outpatient) services and thus both data sources must be used for the most sensitive exposure measurement (Centers for Medicare and Medicaid Services, 2021). Similarly, for EMR data, IV bisphosphonate use that is captured in an EMR separate from the one being leveraged for a study (e.g., a specialist's EMR versus the primary care EMR) typically will not be measured (Strom et al., 2020c).

In general, bisphosphonates accumulate heavily in bone and have long half-lives due to a strong binding of the drug molecules to the bone mineral hydroxyapatite (Nancollas et al., 2006). Thus, after a baseline period of exposure, bisphosphonates continue to suppress bone turnover and protect against fractures after therapy discontinuation. This extended duration of effects is important to consider both for studies of bisphosphonate discontinuation (e.g., drug holiday studies) but also for studies examining drug switching, as residual bisphosphonate exposure may continue to affect bone after the new drug is started. Exposure measurement may therefore need to account for prior use of bisphosphonates, particularly when estimating fracture outcomes. For example, a study in Ontario, Canada found that 80 % of new users of denosumab had prior exposure to bisphosphonates (70 % of these with 3 or more years of prior use) (Ban et al., 2019).

While bisphosphonates are often grouped as one exposure class, there are important intraclass differences in their pharmacokinetics. Detailed reviews on the pharmacologic differences of bisphosphonates as well as how these differences affect clinical considerations for drug holidays have been published (Hayes et al., 2022; Hayes et al., 2021a). The degree of accumulation of drug molecules and duration of binding to hydroxyapatite in bone is dependent on the drug's molecular structure (Russell et al., 2008). For example, alendronate and zoledronic acid bind more potently than risedronate and ibandronate (Nancollas et al., 2006) and have several other features that enhance accumulation and duration of binding to the bone (Russell et al., 2008). We recently identified that, among those undergoing a drug holiday after long-term oral bisphosphonate treatment, treatment with risedronate (versus alendronate) before the drug holiday was associated with a 20 % increased relative risk of hip fracture for drug holidays longer than 2 years' in duration (Hayes et al., 2022). Thus, evidence suggests these pharmacokinetic differences are meaningful for the anti-fracture benefits of bisphosphonates after treatment discontinuation. Duration of treatment before the drug holiday also appeared to modify the risk of fracture during a drug holiday, and so duration of exposure, and potentially the degree of medication adherence, prior to a drug holiday may also be factors to consider when examining bisphosphonate treatment effects upon discontinuation or switching therapy (Hayes et al., 2022). Bisphosphonates also display a differential degree of osteoclast inhibition because of different affinities for the farnesyl pyrophosphate synthase (FPPS) enzyme to induce osteoclast apoptosis, with risedronate having more potency than alendronate, for example (Russell et al., 2008). However, evidence suggests that the pharmacologic differences in FPPS inhibition do not translate to a difference in on-treatment effectiveness between alendronate and risedronate (Curtis et al., 2009; Cadarette et al., 2013).

3.1.2. Denosumab

Denosumab is a biologic, monoclonal antibody therapy that acts as an antiresorptive. Denosumab inhibits receptor activator of nuclear factor kappa-B ligand (RANKL) to induce osteoclast apoptosis (Hanley et al., 2012). Thus, much like bisphosphonates, denosumab improves balance within the bone turnover cycle to increase BMD within 3–6 months of initiating therapy, with fracture risk reduction starting after 8–12 months (Cummings et al., 2009). Denosumab is typically administered subcutaneously by a healthcare provider and dosed every six months; therefore, as with IV bisphosphonates, exposures in encounter data may need to be measured through both prescription medication

and outpatient services claims. In contrast to bisphosphonates, denosumab does not bind to the bone matrix and is only effective when sufficient amounts are circulating to inhibit osteoclast activity (Hanley et al., 2012); denosumab therefore does not have an extended duration of anti-fracture effects beyond its dosing window or after therapy discontinuation. Conversely, evidence demonstrates that there may be an *increased* risk of vertebral fractures after denosumab discontinuation (versus baseline risk or risk with placebo) (Cummings et al., 2018). The "rebound" fracture risk is hypothesized to relate to an accumulation of osteoclast precursors during denosumab therapy that mature into osteoclasts promptly when denosumab is discontinued (Anastasilakis et al., 2021). This increased fracture risk may begin as soon as 2 months after the first missed denosumab dose (Cummings et al., 2018; Florez et al., 2019; Burckhardt et al., 2021). Moreover, the rebound fracture risk may increase with a longer duration of denosumab treatment prior to discontinuation (Anastasilakis et al., 2021; Sosa-Henríquez et al., 2021; Popp et al., 2018); cumulative exposure effects may thus need to be considered in drug effects studies of denosumab discontinuation.

3.1.3. Anabolic treatment

Anabolic treatments for osteoporosis increase BMD and reduce fracture risk via upregulation and increased survival of osteoblasts (Vall and Parmar, 2023). They also exert additional effects on calcium and phosphate homeostasis that may further help to improve bone density and quality (Vall and Parmar, 2023). Onsets of effects on lumbar spine BMD occur within 3 months and within 6 months for femoral neck and total hip BMD (Miyauchi et al., 2010); trials demonstrate significant anti-fracture effects after 8 to 12 months of therapy (Neer et al., 2001).

Teriparatide is a biologic therapy that is an analog of parathyroid hormone (PTH), and abaloparatide is a newer, closely related therapy to teriparatide with similar anti-fracture effects (Sleeman and Clements, 2019). Anabolic treatments likely have more profound effects on improvement of BMD and vertebral fracture risk reduction in glucocorticoid-induced osteoporosis (GIOP) versus primary osteoporosis due to the inhibition of glucocorticoids on osteoblasts (Langdahl et al., 2018). Both teriparatide and abaloparatide are administered subcutaneously once daily, and use of anabolic treatments is recommended to be limited to 24 months or less for a patient's lifetime due to a potential increased risk of osteosarcoma (Eli Lilly Canada Inc, 2020). Because these biologic molecules have relatively short half-lives and do not become part of the bone matrix like bisphosphonates, anabolic therapy effects likely cease shortly after therapy discontinuation (Hodsman et al., 2005). Teriparatide and abaloparatide are usually self-administered by patients, and as such the majority of exposures are likely to be captured through prescription drug claims, though outpatient services claims may capture a modest amount of additional use. Finally, romosozumab is a relatively new therapeutic agent (first approved for use in 2019 in the U.S.). It has primarily anabolic effects, though it has minor antiresorptive qualities as well (Lim and Bolster, 2017). Romosozumab increases BMD by binding to and inhibiting sclerostin, an endogenous molecule that upregulates osteoclast activation and downregulates bone formation (Lim and Bolster, 2017). It is administered subcutaneously once monthly for 12 months maximum by a trained healthcare provider and therefore use may be captured by a mixture of prescription medication and outpatient services claims (Saag et al., 2017).

3.1.4. Other therapies

In brief, other medications used for the treatment of osteoporosis include calcitonin, hormone replacement therapies (HRT), and raloxifene. Calcitonin is an analog of human calcitonin that inhibits osteoclasts and regulates calcium homeostasis (McLaughlin and Jialal, 2022). Nasal calcitonin is available for use in the U.S. for osteoporosis, but is no longer available in many other countries due to a potential increased risk of malignancy (Wells et al., 2016). HRT (e.g., conjugated estrogens) are some of the oldest therapies for osteoporosis that support bone health through the replacement of estrogen. HRT is largely targeted to help manage menopausal symptoms for females (Papaioannou et al., 2010; Levin et al., 2018). However, HRT does not have as potent anti-fracture effects versus other therapies for osteoporosis like bisphosphonates, particularly for non-vertebral fractures (Levin et al., 2018). The use of HRT for osteoporosis has decreased in the last 2 decades, potentially due to concerns about an increased risk of thromboembolism with therapy (Rossouw et al., 2002) combined with the emergence of newer and more potent treatments like bisphosphonates and denosumab. Raloxifene is a selective estrogen receptor modulator (SERM) that binds and activates estrogen-modulated pathways that promote bone health and breast cancer protection (Quintanilla Rodriguez and Correa, 2023). Raloxifene is a daily oral medication that can be prescribed as concomitant therapy with other osteoporosis drugs such as bisphosphonates (Quintanilla Rodriguez and Correa, 2023). Like HRT, its use has decreased in recent years following the emergence of increased risk of thromboembolism and stroke in postmenopausal females at risk for cardiovascular disease (Barrett-Connor et al., 2006).

4. Identifying osteoporosis medication exposures in RWD

4.1. Basic concepts

Measurement of exposure to an osteoporosis drug is based on the presence of a pharmacy dispensing claim or a prescription note within EMR data. The ideal design typically restricts inclusion to patients that are new users of the medication to avoid prevalent user bias (Lund et al., 2015; Yoshida et al., 2015). Following the start of therapy, continued use is tracked via repeated dispensing claims or prescription notes within the database. Indeed, adherence to therapy (persistence, implementation, and long-term therapy, Fig. 1) is estimated based on this follow-up information. In a claims database, adherence is determined by the information on the date of each claim, including: drug name and strength, quantity dispensed, estimated days supplied, and days until next dispensation (when applicable). However, in an EMR, the calculation is based on the date of the prescription note and the dosing instructions provided by the physician. Importantly, in a claims database, the days supply/covered will usually be complete or computable based on dose and quantity. However, days supply information is not always measurable in EMR databases, making it challenging to determine precise exposures.

An additional consideration of measurement of osteoporosis medication exposures in RWD pertains to good data practices, which includes data visualization and cleaning (Baillie et al., 2022). As all RWD are collected for purposes other than research, human-error and institutional restrictions can lead to errors or illogical values. It is beyond the scope of this review to provide a detailed description of data cleaning strategies or database specific considerations. Instead, we emphasize the importance of transparency in reporting – both of the characteristics of the database and any data cleaning strategies, to ensure the results of a study can be replicated (Wang et al., 2017). Initial data analysis is an important step in research, yet is poorly reported (Huebner et al., 2020). We provide some considerations with osteoporosis drug exposure data cleaning, and refer readers to other papers that provide broader context (Burden et al., 2013; Baillie et al., 2022; Huebner et al., 2020; Burden et al., 2015a; Burden et al., 2015b). Table 2 provides examples for logically imputing days covered (days supplied) based on osteoporosis drug strength and quantity (unit) dispensed. For example, one weekly unit of alendronate covers 7 days of therapy, one monthly unit of risedronate covers 30 days, and an annual intravenous infusion of zoledronic acid covers 365 days.

4.2. Measuring treatment adherence

Adherence is an umbrella term used to describe medication taking behavior and is traditionally quantified by measures of persistence and

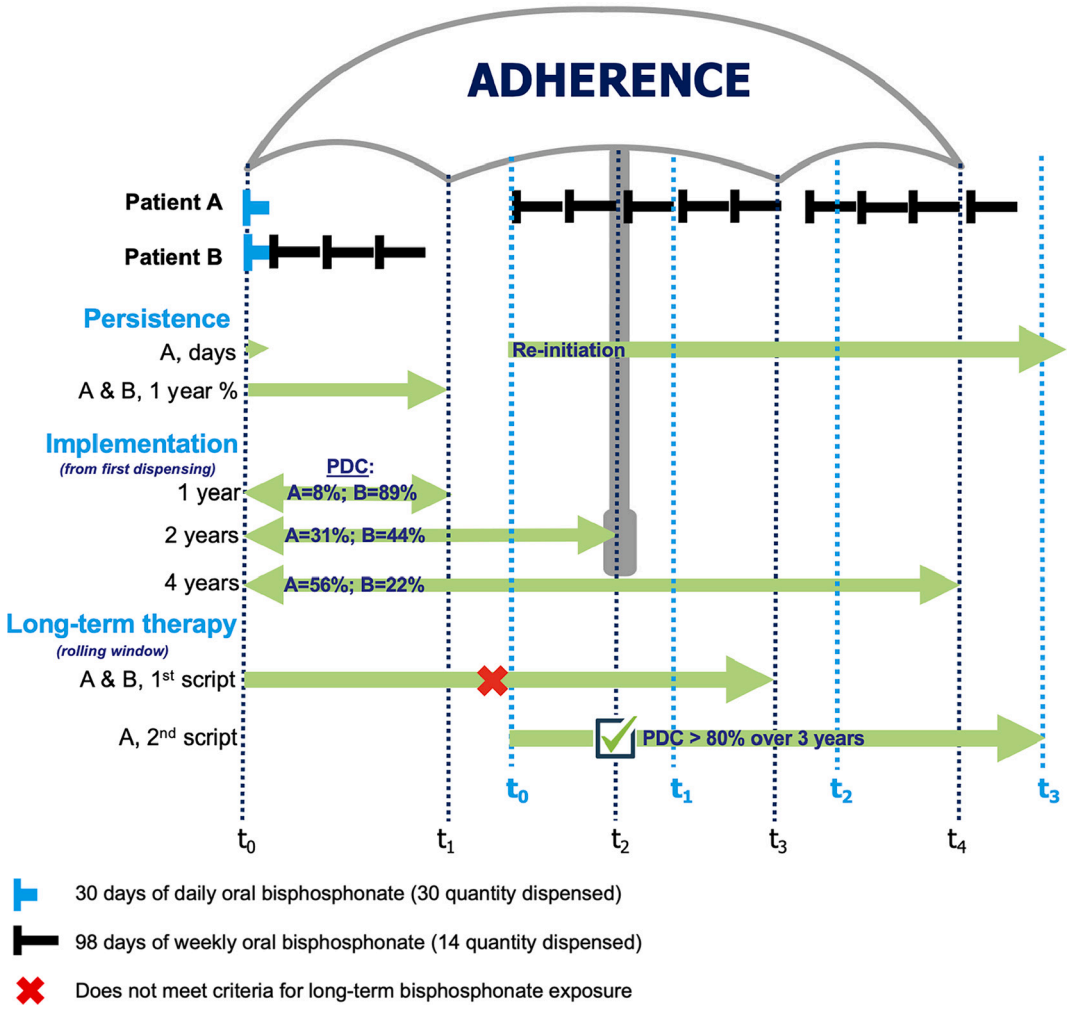

Fig. 1. Visual depiction of adherence measurement.
PDC: Proportion of Days Covered (calculated as number of days covered divided by the number of days within the observation window).

implementation (compliance) (Cadarette and Burden, 2010; Strom et al., 2020d). In the following sections, we also introduce a third measure of adherence that can be used to better capture long-term drug exposure using a rolling-window approach. Fig. 1 visualizes the different measures with two patient case examples. We walk through each type of adherence measure and how the two patient cases can be interpreted.

Adherence is an umbrella term used to describe medication taking behavior and is traditionally quantified by measures of persistence and implementation (compliance). Dotted lines (rain) depict years of follow-up from baseline (t_0) and green arrows depict windows of observation.

A rolling-window is most appropriate to document real-world long-term exposures, here proportion of days covered (PDC) is considered over a 3-year window for each dispensation starting with the first. If the 80 % or more PDC criteria is not met based on the first dispensation, then the window of observation rolls forward to the next dispensation. Patient A meets the criteria for long-term exposure after their second dispensation while Patient B never meets the criteria for long-term exposure.

PDC: Proportion of Days Covered (calculated as number of days covered divided by the number of days within the observation window)

4.2.1. Persistence vs. discontinuation

Persistence is typically based on initial therapy (first exposure identified) and can be quantified by two metrics: a) length of persistence in time (e.g., days), and b) proportion of patients persisting within a specified length of time. Both metrics are based on days covered by the drug before discontinuation. The "permissible gap," "grace period," or "gap length" is decided by the researcher and is a key factor in persistence measurement since it is used to define discontinuation. Logically, the longer the permissible gap and thus lenience in grace period to define persistence, the more patients will be estimated to persist with therapy. It can thus be challenging to compare estimates of persistence between studies that use different gap lengths for deciding treatment discontinuation. Permissible gap length is best based on pharmacology yet also the research question. In outcome studies, the pharmacology is critical to best capture drug exposure and its safety and effectiveness (see Box 1). For health services descriptive research questions, following a common data model may be most appropriate to help compare estimates across databases and different studies. Again, transparency in reporting is critical to support reproducibility (Wang et al., 2017).

Patient A in our case example (Fig. 1) received only a 30 days supply of medication in the first year of observation. A single dispensation is typical for about 20 % of patients that initiate a chronic medication for the first time (Yeaw et al., 2009; Balasubramanian et al., 2013), and makes it difficult to estimate when the patient stopped therapy, or even if any of the medication was taken. Using a 60-day permissible gap, patient A would be estimated to have persisted with therapy for 30 days. However, in some instances, a researcher may crudely take the first and last dates of medication dispensation to estimate treatment length and thus persistence for patient A would be estimated to be over 4 years – refer to long-term exposure section below to appreciate a more sophisticated approach to define long-term therapy.

Table 2
Logical days of drug covered by unit of osteoporosis drug based on strength/regimen.

Drug	Strength	Regimen	Days/unit
Bisphosphonates			
	5 mg, 10 mg	Daily PO	1
	35 mg, 70 mg, 70 mg/75 ml	Weekly PO	7
Alendronate	2.5 mg	Daily PO	1
Ibandronate	150 mg	Monthly PO	30
	1 mg	Daily PO	1
Minodronate	50 mg	Monthly PO	30
	2.5 mg, 5 mg	Daily PO	1
	17.5 mg, 35 mg	Weekly PO	7
	75 mg	Monthly (Japan) PO	30
		2/Month (others) PO	15
Risedronate	150 mg	Monthly PO	30
Zoledronic acid	5 mg/100 ml	Annual IV infusion	365
Selective estrogen receptive modulator			
Raloxifene	60 mg	Daily PO	1
Anti-parathyroid and parathyroid hormone therapies			
Abaloparatide	80 μg	Daily SC injection	30[a]
Teriparatide	250 μg/ml	Daily SC injection	30[a]
Calcitonin	200 U/spray	Daily nasal spray	30[a]
Biologics			
Denosumab	60 mg/ml	Semi-annual SC injection	183
Romozosumab	105 mg/1.17 ml	2 SC injections per month	15

IV = intravenous, PO = per os (by month or orally), SC = subcutaneous.
[a] Each pre-filled syringe (unit) for SC injection and bottle of nasal spray should last 30 days, yet some researchers may reduce to 28 days or fewer acknowledging potential spoilage during patient self-administration (implementation).

Patient B similarly received an initial dispensation of 30 days – one month supply is typical when a patient initiates a new chronic medication to permit follow-up and assessment of drug tolerance by the patient and adjustment as required before committing to extended therapy. Thereafter, a 3-month supply is common. Of interest, patient B picked-up their second dispensation before the first was finished. Here, persistence would be estimated as 324 days (30 + 3*98) if the researcher considered overlap in prescriptions as additive (i.e., presumed that the patient finished their first dispensation before starting their second). However, different assumptions could be made. For example, in this case the patient switched from a daily to weekly bisphosphonate and thus one may presume the patient discarded the inconvenient daily dose. We emphasize here that researchers need to be transparent not only in data cleaning, yet also with assumptions made in calculating measures of treatment adherence.

In addition to length of therapy discussed above, many researchers quantify persistence as the proportion of patients with evidence of continued exposure after a defined length of time, e.g., proportion persisting at 1 year. In this case, patient A did not persist for one year and patient B did, thus 1-year persistence would be estimated at 50 %.

4.2.2. Implementation (compliance)

Implementation is a marker of how well a patient follows the treatment regimen and has traditionally been referred to as compliance. We adopt recent recommendations to preferentially use the word implementation (Strom et al., 2020d; Vrijens et al., 2012), as it does not imply intentional lack of compliance by a patient. Proportion of days covered (PDC) and medication possession ratio (MPR) are common metrics of treatment implementation (Cadarette and Burden, 2010; Strom et al., 2020d). Both are calculated based on the total days covered (supplied) by a drug, over a specified observation window (e.g., 365 days). However, PDC is capped at one (100 %), recognizing that although a patient may have picked-up a prescription and thus have medication on hand, it is unlikely they would consume more than the prescribed regimen.

In our patient examples, **Patient A** received a 30-day supply of daily medication over a year (30/365 = 8 % implementation), yet 30-days plus 2*98 days over 2-years ([30 + 98 + 98]/730 = 31 % implementation). Similarly, the PDC over 4 years would be 56 % ([30 + 98*8]/1460). However, calculating implementation at first-ever dispensing ignores the fact that the patient discontinued treatment and reinitiated therapy for a consistent period after an extended gap. Had the researcher instead calculated implementation measurement at the start of Patient A's treatment re-initiation (3*98 = 392/365), 1-year implementation would be calculated as a PDC of 81 %. This calculation "violates" the new user design, yet given consistent evidence that about 50 % of patients discontinue new therapy for a chronic asymptomatic condition within the first year then return to therapy after an extended gap, failing to consider dispensations after an extended gap underestimates true long-term exposure. We cover the rolling window approach to define long-term treatment exposure in the following section. As a second example, **Patient B** received 30-days covered plus 3*98 days over 1-year (89 % implementation), yet only 44 % over 2-years. Implementation estimates lack clarity in real-world treatment patterns as the PDC and MPR are overall estimates of drug available, yet miss important considerations of gaps in therapy and if treatment had discontinued. Careful consideration of the research question(s), purpose of each measure and limitations of each measure is important.

PDC and MPR are often categorized as good (≥80 %), moderate or medium (50 % < PDC < 80 %), and low or poor (PDC ≤ 50 %) (Burden et al., 2015b; Strom et al., 2020d). However, the decision to define levels of adherence based on implementation is best based on the pharmacology of the drug under investigation, with gaps in exposure to oral bisphosphonates potentially becoming more lenient after a minimum 6-month wash-in, tighter considerations for drugs with short half-lives like raloxifene, and broader considerations for an infusion of zoledronic acid that may be protective longer than 1-year. Indeed, when considering the safety and benefits of osteoporosis medication, pharmacology is critically important in deciding permissible gaps in therapy. See Box 1 for some other considerations when estimating drug exposure effects in outcome studies.

4.2.3. Diving deeper into adherence measurement with some data cleaning considerations

As indicated above and with special considerations in Box 1, many methodological decisions related to exposure measurement will be driven by the underlying research question. Here we walk through a specific example to differentiate between persistence and implementation and highlight potential decision-making points with weekly alendronate using a 60-day permissible gap. In this example, a patient initiates weekly alendronate with the following detail from the pharmacy claim: quantity dispensed = 12, days supply = 90. A point of consideration here is that best practice in data cleaning would be to correct the estimated days supply of 90 (3 months) in the pharmacy claims to 84 (12 weekly pills = 12*7 = 84 days covered). The patient is then dispensed another quantity of 12 weekly alendronate pills 80 days following the initial dispensing date, supporting the initial 12 units (84 days) supplied with a slightly early refill. It is also plausible to assume that the patient picked up their refill of 3-months supply 4 days early and maintained their weekly regimen (i.e., took the first dose of their refill on day 85).

Then, 21 days after they were due for a subsequent dispensing of alendronate based on the days supply of the second dispensing, the patient is dispensed "3" units (quantity) of weekly alendronate with estimated days supply of 90. Although rare, on occasion a pharmacy may indicate the quantity of blister packs instead of the quantity of pills. Given that weekly alendronate is commonly dispensed as 4 pills in a

Box 1
Consideration of days covered and pharmacology in outcome studies.

Adherence is a marker of drug exposure, yet strength and pharmacology are critically important when estimating drug exposure on drug safety and benefits, particularly in the case of bisphosphonates that persist in bone and denosumab that must be carefully implemented.

Case of milligram equivalents of bisphosphonate in addition to length of therapy

Bisphosphonates persist in bone and thus following a 6- to 12-month run-in window, the length of permissible gap could conceivably be stretched. However, the milligram equivalent of drug exposure is another important consideration. Of interest, while alendronate (10 mg daily, 70 mg weekly) and risedronate (5 mg daily, 35 mg weekly, 150 mg or 2 consecutive doses of 75 mg monthly) doses correspond to the same daily equivalent (10 mg alendronate and 5 mg risedronate), monthly treatment with ibandronate (2.5 mg daily, 150 mg monthly) and minodronate (1 mg daily, 50 mg monthly) do not. While the difference is daily equivalent of strength would not make a difference in estimating adherence to the prescribed regimen (e.g., length of persistence or estimates of implementation), the difference in strength would be of interest when considering drug effects. It is beyond the scope of this paper to describe consideration for outcome studies, as the focus is on osteoporosis drug exposure and adherence, yet we note that 30 days of 2.5 mg daily ibandronate is equivalent to 75 mg over 30 days, which is half the dose of the 150 mg monthly dose, and thus cumulative dose is an important consideration in addition to days covered in drug outcome studies. Similarly, to our knowledge, Japan is the only country to use a half dose of alendronate (5 mg daily, 35 mg weekly) and risedronate (2.5 mg daily, 17.5 mg weekly, 75 mg monthly) for treatment, and thus cumulative dose of each medication is important when designing outcome studies. Finally, other than Japan, the 5 mg and 35 mg alendronate is typically prescribed for prevention and thus careful consideration of differences in patient characteristics when bisphosphonates are prescribed for preventing vs. treating osteoporosis must be considered when designing an outcome study.

Case of bisphosphonate discontinuation vs. lasting effects

Clinical trial evidence supports a 3-year drug holiday following 3 annual doses of zoledronic acid. Post-hoc analysis also supports zoledronic acid dosing every 18 months. It can thus be tricky for the researcher to define discontinuation and the meaning of discontinuation. For example, did the patient discontinue after 3 annual doses of zoledronic acid, or are they covered for 6 years? In this case, both are likely true. However, we need RWE to confirm lasting benefits (and harms) following discontinuation of not only for zoledronic acid, yet each bisphosphonate given relative exposure (days and mg equivalent coverage) before discontinuation.

Case of timing and number of denosumab doses

Unlike bisphosphonates that persist in bone and thus permissible gap length may be stretched, denosumab implementation must be carefully followed as delays in therapy as short as 2 months can rapidly lead to bone loss, particularly at the spine that is a metabolically active site for bone turnover. In addition, given that the concern for rapid bone loss is greater with increased persistence (i.e., number of doses and accumulation of immature osteoclasts), the harms of discontinuing or delayed denosumab after a single dose is of less concern than after several doses. Careful consideration of the number of doses and gaps in therapy is thus important when designing a study of the benefits and harms of denosumab therapy.

blister pack, a 90 days supply estimate and the patient's dispensation history, it is safe to assume that the patient received 3 blister packs of 4 pills and thus 84 days supply when conducting data cleaning in this case. The patient therefore has a 21-day or 3-week gap between the second and third dispensings, less than the 60-day permissible gap.

The patient then does not receive a 4th dispensation. Using a 60-day permissible gap, the patient would be estimated to persist with alendronate therapy for 84 + 84 + 21 + 84 = 273 days. Gap days between dispensations within the a priori defined permissible gap are included in the overall estimate of persistence (how long the patient continued with therapy). Here a 3-week gap could indicate that the patient stopped for 3 weeks before picking-up their refill, or that the patient missed 3 weekly doses over the course of the 3 months and thus to their knowledge they were only due to pick-up their refill at 3 weeks after the prior dispensation was supposed to end. It is also possible that the patient did not take all weekly pills in their final dispensation and thus persistence with therapy is overestimated, or that the patient continued to miss some weekly doses yet from their perspective continued to be treated for the full year. The a priori defined permissible gap is critical and must be adhered to when estimating persistence, particularly when comparing estimates between different data sources.

In our example, implementation over the first year since treatment initiation would be estimated as 69 % ([84*3]/365). In the absence of a next refill, the researcher can make some assumptions as to whether the final dispensation was taken to completion. Typically, all dispensations (quantity) are counted when estimating patient implementation of pharmacotherapy. Using consistent metrics facilitates direct comparison to other data sources. Transparency in methodological decisions, including data cleaning, is imperative.

4.2.4. Long-term exposure

RWE on the benefits and harms of long-term exposures to osteoporosis therapy is a critical area of research. Specifically, drug holidays from bisphosphonate therapy are recommended for most patients after 3 to 5 years of continuous exposure. A PDC of 80 % or more over 3 or more years has previously been used to define long-term bisphosphonate therapy (Curtis et al., 2020; Hayes et al., 2022; Hayes et al., 2021b). We believe an 80 % or greater PDC is pharmacologically appropriate for bisphosphonates given the minimum 3-year time period and that bisphosphonates persist in bone. Pivotal trials have also identified fracture benefits with at least 6 months of therapy with this level of adherence (Black et al., 1996; Harris et al., 1999).

While initial adherence may be poor with only about half of patients persisting for a year, more than half of patients that discontinue therapy will reinitiate therapy after an extended gap (Balasubramanian et al., 2013; Burden et al., 2012; Brookhart et al., 2007). To account for stopping and starting patterns with osteoporosis medication when measuring long-term oral bisphosphonate use, such as **Patient A**, we developed a method that uses rolling-windows (Hayes et al., 2021b). In brief, we followed new initiators of oral bisphosphonates for 3-year rolling windows to assess for long-term therapy (≥80 % PDC within the 3-year window). The window shifted by 1 day forward in time until the patient met the criterion for long-term therapy, died, or the end of the study data was reached. Of the patients with long-term treatment, 20 % had a gap between their first prescription and the start of long-term therapy. Thus, examining only initial persistence to oral bisphosphonate

treatment using a simple persistence (new user design) measure *misclassified* many patients as not being exposed to long-term therapy. Use of our novel rolling-window is most appropriate to document real-world long-term exposures. Pharmacy claims data can therefore be an excellent source to identify long-term bisphosphonate exposure with these methods implemented.

In our patient examples, neither patient would be identified as taking long-term bisphosphonates using PDC or MPR based on the first prescription dispensed. For example, here **Patient A**'s 3-year PDC = 47 % ([30 + 98*5]/1095). However, moving forward to the next dispensation and after a gap >1 year in length, **Patient A**'s 3-year PDC = 81 % when following forward 3 years from treatment re-initiation (98*9/1095). Here, long-term bisphosphonate initiation would be defined by the re-initiation date, and entry into a long-term bisphosphonate cohort defined by re-initiation date +1095 days, i.e., the date PDC ≥ 80 % over a 3-year period.

4.2.4.1. Special exposure consideration: measurement of bisphosphonate drug holidays. An essential component of exposure measurement in drug holiday studies is how to define an *intentional discontinuation* of bisphosphonate therapy. In an observational study, this measurement centers around a requirement that a patient stop therapy after a baseline period of exposure (e.g., 3 years; see section above on defining long-term therapy) for a pre-defined duration of time. Of note, for studies examining the effects of drug holidays compared to time on-treatment (i.e., discontinued vs. continued bisphosphonate treatment or therapy switching), only those meeting the prespecified definition of long-term therapy are eligible for study. Person-time before meeting the criteria for a drug holiday cannot be classified as drug holiday-exposed to avoid immortal time bias (Suissa, 2008).

Many observational studies require that patients cease bisphosphonate treatment for one year or longer before follow-up begins. For bisphosphonates with a long duration of effects as demonstrated in clinical trials (Black et al., 2006) or very intermittent dosing (Reid et al., 2013), like zoledronic acid, this longer window to ascertain drug holidays may be acceptable. However, using this long of a window to define a drug holiday may differentially exclude fractures and other outcomes that can occur during shorter periods after discontinuation. We propose that observational studies leverage a shorter ascertainment window to first identify persons early into long-term therapy discontinuation, then exclude patients with indicators of "sick stopping." (Glynn et al., 2001) For example, in a recent study of drug holidays that leveraged claims data, we first identified persons with 120 consecutive days without bisphosphonate therapy after a period of long-term therapy (Hayes et al., 2022). We then excluded those who were likely stopping treatment for reasons other than a drug holiday that we were able to identify within these 120 days: those who switched to another osteoporosis treatment, died, entered long-term care, or experienced an osteoporotic fracture. One might also consider whether a clinic visit occurred within a certain period of time prior to the start of this gap in treatment to further refine the drug holiday exposure definition. Using this approach to define potential drug holidays, included persons who later resumed osteoporosis therapy were off therapy for 1.8 years on average, generally the recommended duration of a drug holiday (1–3 years) (Hayes et al., 2022).

4.3. Treatment switching

Sankey plots that document patient flow between treatment options is gaining popularity in the field of pharmacoepidemiology to visualize treatment transition and switching patterns (Gatto et al., 2022). Fig. 2 presents the Sankey plot of 6-month treatment transitions in the cohort

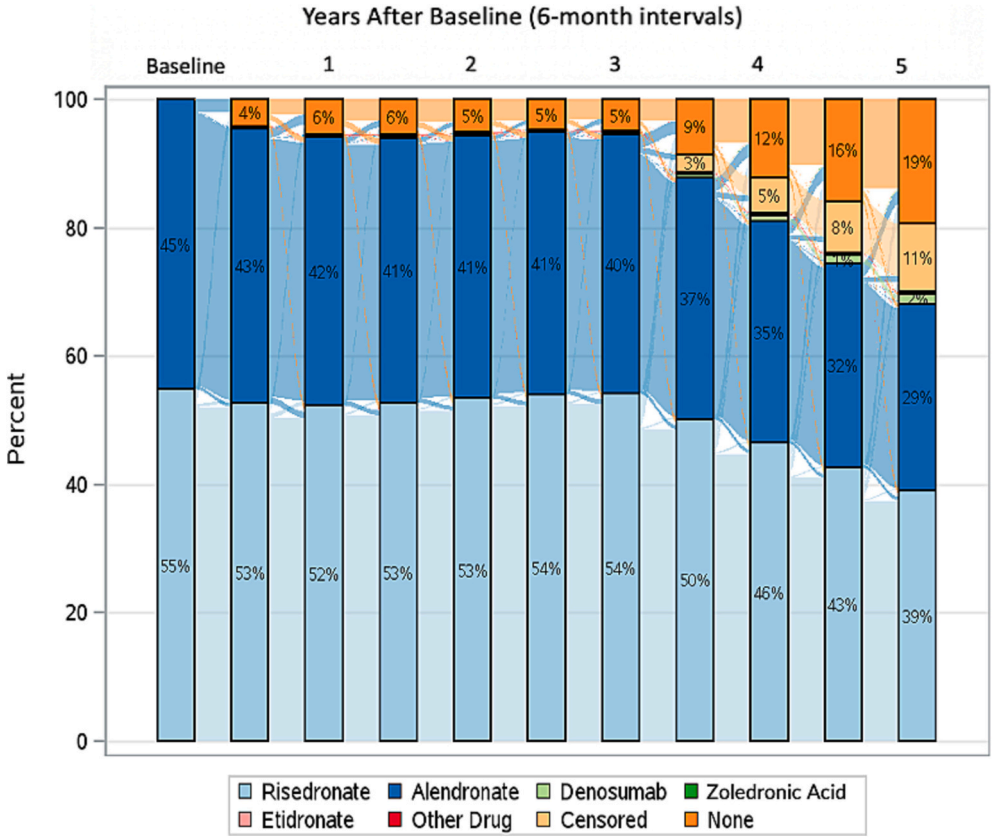

Fig. 2. Sankey plot demonstrating 6-month switching patterns between osteoporosis pharmacotherapies or discontinuation and reinitiating in a cohort of patients treated with long-term oral bisphosphonate therapy (3+ years with proportion days covered ≥80 % using rolling window approach), n = 120,368 (Hayes et al., 2021b).

of 120,368 older adults in Ontario achieving long-term oral bisphosphonate (3 or more years with PDC 80 %) status (Hayes et al., 2021b). These data were linked using unique encoded identifiers and analyzed at ICES. As depicted in the Sankey plot, few patients switched between alendronate or risedronate as most patients continued with the oral bisphosphonate initiated when they continued to persist for a minimum of 3 years. The Sankey plot also helps demonstrate that over time, more patients stopped therapy (e.g., initiated a bisphosphonate drug holiday), switched to denosumab, or were censored due to loss of follow-up.

5. Conclusion

Using RWE to fill knowledge gaps in osteoporosis medication use and effects is important, yet observational studies must carefully consider issues of exposure measurement to minimize bias and improve the accuracy of conclusions from this RWE. Proper exposure measurement of osteoporosis medications is a critical foundation for the validity of any observational study of these medications, including adherence and utilization. These considerations are especially critical for RWE on osteoporosis medication effects on clinical outcomes to have valid measures of exposed versus unexposed time and exposure-outcome timing that is necessary to measure medication effects on outcomes. Observational studies must consider the advantages and disadvantages of osteoporosis medication measures in the specific RWD source used, the unique pharmacology of different osteoporosis medication classes, gaps in treatment and switching between therapies, and the specific outcome being studied.

CRediT authorship contribution statement

Kaleen N. Hayes: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization. **Suzanne M. Cadarette:** Writing – review & editing, Funding acquisition, Conceptualization. **Andrea M. Burden:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

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Data availability

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