



RESEARCH ARTICLE

Use and risk of side effects of antiresorptive medication in people with intellectual disabilities [version 1; peer review: 2 approved]

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Abstract

Background:

Recent studies show that adults with intellectual disabilities (ID) have high incidence of major osteoporotic fracture, especially hip fracture. In those ≥ 50 years, women and men with ID have an approximately two and four times higher rate of hip fracture than women and men without ID. Increased awareness of osteoporotic fracture risk in ID may lead to wider use of antiresorptive drugs (bisphosphonates and denosumab) in this population. We aimed to compare, between people with and without ID, the incidence of 1) major side effects, namely medication related osteoporosis of the jaw (ONJ) and oesophagitis; 2) oral pathology, which can be a risk factor for ONJ.

Methods:

Exploratory study investigating safety of first line osteoporosis medication within the population of a previous study comparing fracture incidence in people with and without ID in the GOLD database of the Clinical Practice Research Datalink 1998–2017.

Results:

The percentage of people on antiresorptive drugs was identical in the ID and non ID group (1.4%). The number of individuals who developed ONJ and oesophagitis during the study was too low to allow an accurate estimate of incidence of the events and a comparison

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between the two groups. The incidence of any oral pathology was 119.31 vs 64.68/10000 person year in the ID vs non ID group.

Conclusions:

Medication related ONJ and oesophagitis are rare in people with and without ID. There is no reason based on our findings to use antiresorptives differently in people with ID as in the rest of the population. However, the potential for side effects of antiresorptives will inherently increase with wider use of these drugs. Given the higher incidence of oral pathology in people with ID, which could put them at higher risk of ONJ, precautions should be taken to prevent this complication by attention to oral health.

Plain English summary

Fracture rates have recently been shown to be substantially higher in people with intellectual disabilities (ID). This finding is likely to lead to the wider use of bone strengthening (antiresorptive) agents in this group, namely bisphosphonates and denosumab. These drugs are effective at reducing the risk of fractures, but carry potential adverse effects. One of these is the rare but serious condition osteonecrosis of the jaw (ONJ). We studied general practice records to investigate whether the incidence of this problem is higher in people with ID taking these drugs. We also looked at the incidence of oral conditions that may put an individual at higher risk of it, including periodontitis, dental abscess, and tooth extractions. The recording of ONJ in people with ID was extremely low, no different from the general population in our study, although we were using general practice rather than dental records. However, dental problems that might predispose to it were recorded nearly twice as frequently in the group with ID. The other side effect we looked at was oesophagitis, which was not found to be more common in people with ID taking bisphosphonates. This study highlights the need to provide good oral hygiene, dental care and surveillance in people with ID receiving antiresorptive drug therapy.

Keywords

Intellectual disabilities; osteoporosis; antiresorptives; bisphosphonates; denosumab; osteonecrosis of the jaw; oesophagitis

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Plain english summary

Fracture rates have recently been shown to be substantially higher in people with intellectual disabilities (ID). This finding is likely to lead to the wider use of bone strengthening (antiresorptive) agents in this group, namely bisphosphonates and denosumab. These drugs are effective at reducing the risk of fractures, but carry potential adverse effects. One of these is the rare but serious condition osteonecrosis of the jaw (ONJ). We studied general practice records to investigate whether the incidence of this problem is higher in people with ID taking these drugs. We also looked at the incidence of oral conditions that may put an individual at higher risk of it, including periodontitis, dental abscess, and tooth extractions. The recording of ONJ in people with ID was extremely low, no different from the general population in our study, although we were using general practice rather than dental records. However, dental problems that might predispose to it were recorded nearly twice as frequently in the group with ID. The other side effect we looked at was oesophagitis, which was not found to be more common in people with ID taking bisphosphonates. This study highlights the need to provide good oral hygiene, dental care and surveillance in people with ID receiving antiresorptive drug therapy.

Introduction

Major epidemiological studies have shown that people with intellectual disabilities (ID) have higher incidence of fracture than their general population counterparts¹⁻⁴. In the latest and most comprehensive of these studies¹ the difference was particularly evident for major osteoporotic fractures, especially hip fracture. In those aged 50 years and over, women with ID had a 2.3 times higher rate and men a 3.8 times higher rate of hip fracture compared to women and men without ID. In younger age groups, differences were even larger.

The increased awareness of a raised fracture risk in people with ID may lead to a wider use of treatment for osteoporosis in this population, particularly of bisphosphonates as these are the first line treatment⁵⁻⁷.

One rare but serious side effect of treatment with antiresorptive agents (bisphosphonates and denosumab) is medication-related osteonecrosis of the jaw (ONJ). Currently, this is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial area that has persisted for longer than eight weeks, in a patient who has been treated with antiresorptive or antiangiogenic medication, without a history of radiation therapy to the jaws or obvious metastatic disease⁸. Reported overall incidence rates of ONJ in people taking bisphosphonates for osteoporosis vary widely, between 0.1–2.5 per 10,000 patient years⁹⁻¹². However, oral procedures, use of prostheses, and periodontitis are risk factors for the development of ONJ^{13,14} in people taking antiresorptives for osteoporosis. In particular, tooth extractions and the presence of periodontal disease increase the risk of ONJ by approximately ten and fivefold respectively^{11,15}.

People with ID have been repeatedly shown to have very poor oral health, including high rates of periodontitis and tooth extractions^{16,17}, hence they could be particularly at risk of ONJ.

Oesophagitis is another important complication of oral bisphosphonate treatment¹⁸, which also has the potential to limit adherence to treatment.

As bisphosphonates are the first line drugs for osteoporosis, we aimed to compare two major side effects, namely medication related osteonecrosis of the jaw (ONJ) and oesophagitis, in people with and without ID. We also aimed to compare the incidence of oral pathology, which can be a risk factor for the development of ONJ, between the two groups.

Methods

The current study is based on the cohort originally extracted for our previous study in the GOLD database of the Clinical Practice Research Datalink (CPRD^{19,20}), which compared fracture incidence rates in people with and without ID¹. In that study we extracted the anonymised health records of all children and adults with ID (n= 73,420) in this database (1998–2017) and five control subjects per patient (n= 367,187), matched by age and gender. The present study is based on this original cohort rather than the proportion with data linked to the hospital episodes statistics (HES) database, as in the published study¹. The study protocol was approved by the Independent Scientific Advisory Committee of the Medicine and Healthcare Products Regulatory Agency (Protocol 18-186RA).

The study population was restricted to those who spent some time in the study at age ≥ 18 years. Individuals entered the study at the latest of their 18th birthday, 1 January 1998 and the date of recording one-year of data in their current GP practice. They were followed up until the earliest of: 31 December 2017, the last date at which their practice contributed data to the CPRD GOLD database, or the date at which the participants died or left their practice. We identified the date of starting treatment with an antiresorptive agent, a bisphosphonate or denosumab. Treatment was defined as having received a minimum of two consecutive prescriptions for a bisphosphonate or denosumab (except for zoledronate, for which one prescription sufficed). People starting on treatment prior to their index date were dropped from the cohort.

We investigated the following outcomes:

- 1) Osteonecrosis of the jaw in people with and without ID exposed to antiresorptives at any time during the study
- 2) Oral conditions, procedures and use of services potentially indicating the presence of ONJ in people with and without ID according to having been exposed or not to treatment with antiresorptives at any time during the study
- 3) Any oral pathology, procedure and use of services that could potentially indicate or be a risk factor for ONJ in the ID vs non ID group as a whole and according to having been exposed or not to treatment with antiresorptives at any time during the study
- 4) Oesophagitis in people with and without ID exposed to bisphosphonates within the previous six months

In order to analyse incidence rates during the study follow-up period, we excluded all individuals with a recorded history of the outcome of interest prior to entering the study.

Definitions of outcomes

1) The term “Medication related osteonecrosis of the jaw” (or “Osteonecrosis of the jaw” without further specification) does not exist as such in the CPRD GOLD database. Hence, the nearest term, i.e. “Osteonecrosis due to drugs” (Read code N334900) was used. We assumed that any such terms found in a patient’s record following exposure to antiresorptives would indicate ONJ.

2) Conditions, procedures and use of services potentially indicating the presence of ONJ were defined by illness codes, e.g. Oral fistula, Jaw diseases, and by service user codes, e.g. Seen in oral surgery clinic, Operation on jaw.

3) Any oral pathology, procedure and use of services included any pathological condition of the oral cavity (except for cancer and salivary lithiasis) and was defined by illness codes, e.g. Dental abscess, Periodontitis, and by service user codes, e.g. Extraction of tooth, Seen by dental surgeon.

Statistical analyses

Exposure to antiresorptive medication was treated as a time varying exposure. In other words, patients were considered unexposed until the date they fulfilled the criterion for receiving this medication. From this date until they developed the outcome or were censored they were assumed to be exposed. Incidence rates and 95% CI for each outcome were calculated using the Stata (version 16) *strate* command²¹. The same analyses could be done with R (R Core Team 2022. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

URL <https://www.R-project.org/>. The incidence rates were stratified by having ID or not, and by exposure to antiresorptive medication or not.

For analysis of the osteonecrosis of the jaw and of the oesophagitis outcome the population was restricted to those taking antiresorptive medication. Patients were followed up from the date of starting medication.

Results

The study population and the prescribed antiresorptive medication are shown in Table 1. The percentage of people on antiresorptive medication was very similar in the ID (1.41%) compared to the non ID group (1.43%). The majority of people in either group were taking a bisphosphonate. Of these, only three in the ID and twelve in the non ID group were taking zoledronate. The median age at treatment start was 60.3 vs 68.4 years in people with ID compared to those without ID.

The number of individuals who developed ONJ during the study was too low to allow an accurate estimate of incidence of the event and a comparison between the two groups.

The incidence of ONJ and ONJ indicative outcomes by group is shown in Table 2. There was a significant difference in both the ID and non ID group between those who had been exposed to antiresorptives and those who had not, with overall rate ratio (95% CI) 2.17 (1.83–2.58).

The incidence of any oral pathology in people not exposed to antiresorptives was 119.31 vs 64.68/10000 person year in the ID vs non ID group, with a rate ratio (95%CI) of 1.84 (1.78–1.91). There was no difference in the ID group between those who had been exposed to bisphosphonates and those who had not (Table 3).

There was a total of only 24 people out of 4445 taking a bisphosphonate, who developed oesophagitis within six months

Table 1. Study population and prescribed antiresorptive medication.

	People with ID		People without ID	
	Total number		Total number	
	59,935		292,498	
Female	24,241	40.4%	120,085	41.1%
Median age at index (10th-90th percentile)	30.1 (18.0-57.5) years		29.5 (18.0 56.9) years	
	Number of people on drug	% of people on drug	Number of people on drug	% of people on drug
Any bisphosphonate	843	1.41%	4,167	1.42%
Zoledronate	3	0.005%	12	0.004%
Denosumab	9	0.01%	48	0.02%
Any of the above*	847	1.41%	4,189	1.43%
Median age (10th-90th percentile)#	60.3 (38.6-77.8) years		68.4 (52.0-82.5) years	

*Eight people with ID and 40 without ID had more than one type of medication

#Age at start of antiresorptive treatment

Table 2. Incidence rate (95% CI) of ONJ and ONJ indicative outcomes in individuals with and without ID according to antiresorptive medication.

	Number of events	Follow-up*	Rate [#]	Lower CI	Upper CI
People with ID never on antiresorptives	1311	43.03	30.47	28.86	32.16
People with ID exposed to antiresorptives	17	0.39	43.72	27.18	70.33
People without ID never on antiresorptives	4790	221.30	21.66	21.05	22.28
People without ID exposed to antiresorptives	115	2.26	50.98	42.46	61.20

* 10,000 years [#]number of events/10,000 person year

Table 3. Incidence rate (95% CI) of any oral pathology in individuals with and without ID according to antiresorptive medication.

	Number of events	Follow-up*	Rate [#]	Lower CI	Upper CI
People with ID never on antiresorptives	4538	38.04	119.31	115.89	122.83
People with ID exposed to antiresorptives	40	0.33	120.71	88.54	164.56
People without ID never on antiresorptives	13506	208.80	64.68	63.60	65.78
People without ID exposed to antiresorptives	195	2.09	93.39	81.16	107.46

* 10,000 years [#]number of events/10,000 person year

of treatment (0.54%). There were too few in the ID group to make a meaningful statistical comparison.

Discussion

This is the first study investigating the use and risk of side effects of antiresorptive medication in people with intellectual disabilities.

The proportion of the cohort prescribed such medication was identical (1.4%) in people with and without ID. However, median age at first prescription was only 60 years, i.e. eight years lower in people with ID. A recent study has shown a higher incidence of major osteoporotic fracture, in particular hip fracture, and a younger age at fracture in people with ID than their general population counterparts¹. Hence, the current finding of the same prescription rate of antiresorptive medication between those with and without ID, implies a lack of awareness of the problem of osteoporosis in people with ID. The younger age at first prescription could be due to the occurrence of fractures at an earlier age. This could lead to prescription of osteoporosis medication for secondary prevention of fracture in younger individuals within the group with ID.

As expected, the vast majority of people in both groups had been prescribed an oral bisphosphonate, with very few having been prescribed zoledronate, or denosumab.

In those treated with antiresorptives, the number of people who developed ONJ was too low for an accurate estimate and for

a valid statistical comparison between the ID and non ID group. The same should be said for the incidence of oesophagitis within six months of bisphosphonate treatment.

However, those who had been exposed to antiresorptives had an approximately twofold higher incidence of outcomes that could possibly indicate the development of ONJ than those who had not. This was similar in the ID and non ID group.

Additionally, people with ID had an almost twofold higher rate of oral pathology than people without ID. This confirms findings of previous studies^{16,17} and coincides with observations from clinical practice.

This study has a number of strengths and limitations. Its main strengths lie in it being the first study to focus on the subject, and in the sample size of the population available for study. The use of the Clinical Practice Research Datalink is a strength as its data originate from a national health system with full coverage of the population, and this database has been used in numerous national and international studies.

However, this is also the study's main limitation as the data are drawn from general practice rather than from dental records. Dentists rather than general practitioners are the main providers of dental care in the UK, hence undercounting of clinical events in a general practice database must be assumed. Whether this would affect one of our study groups more than the other, thus creating recording bias, is unknown. On the other

hand, our results showing an excess of oral pathology in people with ID are in line with previous literature^{16,17} and wide clinical experience.

Another limitation of the study is the years it represents, namely 1998–2017. Osteonecrosis of the jaw as a side effect of bisphosphonates was first reported in the scientific literature in 2003²², and it would have taken some time before clinicians would become aware of it. This is exemplified by the fact that in the CPRD GOLD database, the term ONJ does not exist as such and that we had to use the nearest term “Osteonecrosis due to drugs” and assume that it would represent ONJ when found in the records of people exposed to bisphosphonates. We tried to mitigate this limitation by analysing also the oral events and procedures that could possibly indicate the underlying presence of ONJ.

Finally, this was an exploratory study based on post-hoc analyses. Although the original cohort was matched on age and gender some of the matching may have been broken in development of the current cohort and in the time –dependent analysis. We did not extract information on any other potential confounders and only generated crude incidence rates.

Despite its major limitations, we believe the study could convey a robust clinical message. Although we are unable to quantify the incidence of antiresorptive related ONJ per se, we found a two-fold incidence of ONJ potentially indicative outcomes in those exposed to bisphosphonates compared to those who were not, the excess being similar in the ID and non-ID group. These outcomes included codes for Oral fistula, Jaw diseases, Seen in oral surgery clinic, Operation on jaw, some of which could possibly point to the underlying presence of ONJ in a database in which the code for this specific pathology does not exist. The coding of the data does not allow further characterisation of these events. The fact that their absolute rates do not differ between the ID and non-ID group may suggest that the incidence of antiresorptive induced ONJ could be similar between people with and without ID. On the other hand, the rates of any oral pathological conditions or procedures were twice as high in people with than without ID. This means that the population at risk of ONJ is proportionally much larger in the ID group and that prescription of antiresorptives should be accompanied by attention to oral health in this population. It is particularly important that oral hygiene is promoted, oral health is assessed, and that any planned dental procedures are carried out before starting treatment with antiresorptive medication^{5,6,22,23}. When procedures, e.g. tooth extractions, need to be performed during treatment, evidence is emerging

that the use of specific surgical protocols may offer protection against post-extraction development of ONJ^{24–26}.

In conclusion, medication related ONJ and oesophagitis are rare in people with and without ID. There is no reason based on our findings to use antiresorptives differently in people with ID as in the rest of the population. However, the potential for side effects of antiresorptive medications will inherently increase with the wider use of these drugs. Given the higher incidence of oral pathology in people with ID, which could put these individuals at higher risk of medication related osteonecrosis of the jaw, precautions should be taken to prevent the development of this complication.

Data availability

Underlying data

We used data from the GOLD database of the Clinical Practice Research Datalink (CPRD). CPRD rules prohibit researchers from sharing datasets. However, the study could be replicated by acquiring the same datasets (see <https://cprd.com/> for access rules) and applying the same code lists used in the study

Extended data

Figshare: Read codes and CPRD GOLD codes for intellectual disabilities, <https://doi.org/10.6084/m9.figshare.21603345.v1>²⁷.

Figshare: Read codes and CPRD Gold codes for oral pathology, <https://doi.org/10.6084/m9.figshare.21608475.v1>²⁸.

Figshare: STROBE checklist for Use and risk of side effects of antiresorptive medication in people with intellectual disabilities, <https://doi.org/10.6084/m9.figshare.21610386.v1>²⁹.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/).

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Zoe Paskins 

Keele University, Keele, England, UK

This manuscript reports a retrospective cohort study in a large UK database of primary care records, exploring incidence and risk factors for side effects of bisphosphonates in people with intellectual disabilities. The manuscript is well written, and I have only minor comments.

The plain English summary includes some technical/long words (e.g. periodontitis, surveillance) and long sentences, and readability could therefore be improved by addressing these points.

In the results and discussion, the authors report small numbers of patients are taking zoledronate. This should be reworded to state 'recorded as taking'. As zoledronate is a hospital prescribed drug this will be under recorded and this should also be added to the limitation section.

I would suggest adding the hypothesis to the abstract i.e. that people with ID have poorer dental/oral health and are therefore at more risk of adverse events associated with bisphosphonates.

I was slightly confused by what was medication related ONJ (MRONJ) and what was non medication related. It appears that codes were searched for MRONJ but results suggest a number of cases were thought to be non-medication related – can the authors comment on this and review use of ONJ throughout to see if MRONJ would be a more suitable acronym in places?

The observation that there are less oral health issues in people without ID taking bisphosphonates, than those taking bisphosphonates, might suggest that as a result of informed decision making, those with oral health issues are more likely to avoid this class of drug. As rates of oral health problems do not differ in people with ID taking, or not taking bisphosphonates, does this suggest this informed decision making may not be happening?

With regards to the entry in discussion pasted below, I wondered if this could be added to methods/results?: *Although we are unable to quantify the incidence of antiresorptive related ONJ per*

se, we found a two-fold incidence of ONJ potentially indicative outcomes in those exposed to bisphosphonates compared to those who were not, the excess being similar in the ID and non-ID group. These outcomes included codes for Oral fistula, Jaw diseases, Seen in oral surgery clinic, Operation on jaw, some of which could possibly point to the underlying presence of ONJ in a database in which the code for this specific pathology does not exist.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Applied health and clinical research in osteoporosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 July 2023

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Kara Anderson 

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Thank you for your paper entitled 'Use and risk of side effects of antiresorptive medication in people with intellectual disabilities'. This manuscript provides rates of medication use and indicative rates of side effects in a large sample size of individuals with and without intellectual disabilities and provides some clinical guidance as to how to utilise these medications in the

specific population.

The paper is overall very clear and well written. My primary suggestion is to provide better detail about the cohort within the manuscript, rather than relying on previous manuscripts for this detail, for example:

- As the cohort is drawn from a clinical database, how is that database managed, how do individuals end up on the database etc.
- How were intellectual disabilities defined for the purpose of the cohort?

Some other broad suggestions I had were to streamline the abstract slightly to improve story (I think the plain language summary tells a better story than the formal abstract); and to provide oral health totals for the whole cohort in addition to by exposure or not to bisphosphonates, as this would also strengthen your conclusions and story. The logical leap is there, but directly providing that data would be helpful.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: epidemiology; technologies for assessing bone health; cohort studies for bone health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
