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Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention: a Systematic Review

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Disclaimers

- Presentation based on Minnesota EPC research under contract to AHRQ. Findings and conclusions are those of Minnesota EPC, and may not represent AHRQ views.
- No financial interests or relationships with commercial entities.
- No discussion of unlabeled or investigational product uses.
- Presentation based on peer-reviewed draft report.

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Background

- Osteoporosis is a skeletal disorder of low bone mass and microarchitectural deterioration of bone, leading to bone fragility and increased risk of fracture (Fx).
- Osteoporosis affects >10 million US adults
- 2 million US adults experience osteoporotic Fx each year
- Osteoporotic Fx cause pain, disability, and impaired QoL, increase healthcare costs; hip and clinical vertebral Fx (CVF) increase mortality

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Short-Term ODT Fx Efficacy: Summary

- RCTs show several FDA approved osteoporosis drug treatments (ODT) reduce short-term Fx risk (≤3 yrs) in PM women w osteoporosis

Drug	NVF	Hip	VF
Alendronate, Risedronate, Zoledronate	↓	↓	↓*
Ibandronate	↓	↔	↓
Raloxifene	↔	↔	↓
Estrogen, Estrogen/Progest	↓	↓	↓
Denosumab	↓	↓	↓
Teriparatide	↓	↔	↓
Abaloparatide	↓	0	↓RVF only

*Zoledronate also lowers risk of incident RVF in men with osteoporosis

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Background

- Few patients with osteoporosis receive ODT
  - E.g., <20% receive ODT in the 1 yr after hip Fx
- Undertreatment of appropriate patients is likely contributing to preventable hip Fx, morbidity, deaths

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Background

- Bisphosphonates (BP) and denosumab associated with rare atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ)
- Recent studies raise concerns about possible rebound Fx after stopping denosumab
- Raloxifene and hormone therapy increase risk of venous thromboembolism (VTE) and stroke (CVA)

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Background

- Benefits and harms of long-term ODT (>3 yr) and ODT holidays are unclear
- Understanding factors that modify likelihood of benefit and harms with long-term ODT and ODT holidays may inform treatment decisions

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Systematic Review

- Reviewed evidence on benefits & harms of long-term osteoporosis drug therapy (ODT) and ODT holidays in men and PM women ≥50 yrs with osteoporosis or osteopenia, & on factors that may modify these effects.

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Methods

- **Search:** Electronic databases 1/1995-6/2018, systematic review references
- **Populations:**
  - Adults ≥ 50 yr with past ODT for osteoporosis or osteopenia to prevent Fx
  - For rare harms, included regardless of osteoporosis status
  - Excluded known 2° osteoporosis, metastatic cancer, bone healing

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Methods

- **Treatment:**
  - Long-term ODT defined as >3 yrs
  - ODT holiday defined as stopping ODT ≥ 1 yr after prior ODT ≥ 1 yr
  - FDA approved for osteoporosis treatment or prevention
- **Study Designs:**
  - RCTs, CCTs
  - Controlled obs studies ≥ 1000 participants for harms (≥100 for rare harms)

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Methods

- **Efficacy outcomes:**
  - 1°: Incident clinical Fx (any [CF], hip, nonvertebral [NVF], vertebral [CVF])
  - 2°: Incident radiographic vertebral Fx (RVF)
- **Harms Outcomes:**
  - Atypical femoral Fx (AFF)
  - Subtrochanteric/femoral shaft Fx w/o confirmed radiographic AFF features (ST/FS Fx)
  - Osteonecrosis of the jaw (ONJ)
  - Serious adverse events (SAE)

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Methods

- **Possible effect modifiers:**
  - Patient: age, sex, race, osteoporosis category, Fx history, FRAX® score, comorbidities
  - Bone: BMD, bone turnover markers
  - ODT: dose, frequency, duration, route

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Key Question 1

- What is the efficacy of long-term (>3 years) ODT in reducing risk of incident fracture (Fx)?
  - Does efficacy of long-term ODT for reducing risk of incident Fx vary by patient, bone, or ODT characteristics?

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Long-Term ODT Fx Efficacy: Summary

Drug	Population	CF	NVF	Hip	CVF	RVF
Alendronate	Osteoporosis (BMD)	↓	↔?	↓?	0	↓
	Osteopenia	↔	↔?	↔	0	↓?
Zoledronate	Osteopenia/osteoporosis	↓	↓	↓?	↓	0
	Osteopenia	↓?	↓	0	↓?	0
Raloxifene	Osteoporosis (BMD/RVF)	↔	↔	↔	↓	↓
Denosumab	Osteopenia/osteoporosis	0	0	0	0	0
Estrogen	Unselected by BMD or Fx	↓	0	↓	↓	0
	Past Fx	↓	0	↓	0	0
Estrogen/ Prog	Unselected by BMD or Fx	↓	0	↓	↓	0
	Past Fx	↓	0	↓?	0	0

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Key Question 2

- What are the harms of long-term (>3 years) ODT?
  - Do harms of long-term ODT vary by patient, bone, or ODT characteristics?

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Long-Term ODT Harms: Summary

Drug*	AFF	ST/FS Fx	ONJ	ONJ dx codes	SAE	VTE	CVA	Death
Alendronate	0	↑?	↑?	↑?	↔?	0	0	↔
Zoledronate	0	0	0	0	↓?	0	↔	↓?
Bisphosphonate	↑	↑	0	0	0	0	0	0
Raloxifene	0	0	0	0	↔	↑	↔	↓?
Estrogen	0	0	0	0	0	↔	↑	↔
Estrogen/Progestin*	0	0	0	0	0	↑	↑?	↔
Denosumab	0	0	0	0	↑?	0	0	0

*Also suggested possible increased risk of dementia, CHD and invasive breast cancer.

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Key Question 3

- What are the benefits and harms of ODT holidays?
  - Do benefits and harms of ODT holidays vary by patient, bone, or ODT characteristics?

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ODT Holiday Fx Effects & Harms: Summary

	Fx Effects					Harms				
Drug*	CF	NVF	Hip	CVF	RVF	AFF	ST/FS Fx	ONJ	ONJ dx codes	SAE
Alendronate	↔	↔	↔	↓?	↔	0	0	0	0	↔
Zoledronate	↔	↔	0	0	↓	0	0	0	0	↔
Bisphosphonate	0	0	0	0	0	0	0	0	0	0
Raloxifene	0	0	0	0	0	0	0	0	0	↔
Estrogen	0	0	0	0	0	0	0	0	0	0
Estrogen/Progestin	0	0	0	0	0	0	0	0	0	0
Denosumab	0	0	0	0	0	0	0	0	0	0

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Conclusions

- Short-term ODT reduces risk of NVF, VF, hip Fx 20-60%
- Long-term ODT reduces risk of VF, but not NVF
- Initiation of ODT in appropriate patients is low
- Risk of AFF & ONJ increased with long-term BP use
- Limited data to guide long-term ODT & drug holidays
- Substantial additional research needed to address knowledge gaps

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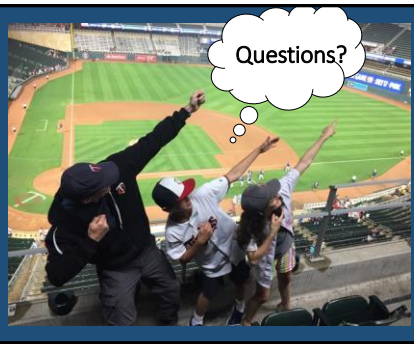

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Reserve Slides

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Strength of Evidence (SOE)

- **Overall SOE for the estimate of effect for each outcome for each treatment comparison based on domains of study limitations/ROB, directness, consistency, precision, and reporting bias**

Rating	Explanation
High	High confidence estimate close to true effect, findings likely stable
Moderate	Moderate confidence estimate near true effect, some deficiencies in evidence, findings likely stable, but some doubt
Low	Low confidence estimate close to true effect, major or numerous deficiencies in evidence, more evidence needed to conclude findings stable
Insufficient	No evidence, unable to estimate effect, or no confidence in estimate of effect

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Alendronate—Long-term efficacy

- **4-yr RCT (n=4432), postmenopausal (PM) women aged 54-81 yr, osteoporosis/osteopenia by BMD, no baseline RVF**

Population	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Osteopenia/ osteoporosis	RVF	0.56 [0.39, 0.80]	-2 [-3, -1]	High
	CF	0.86 [0.73, 1.01]	-2 [-4, 0]	Mod
	NVF	0.88 [0.74, 1.04]	-1 [-3, 0]	Mod
	Hip Fx	0.79 [0.43, 1.44]	-0.2 [-0.8, 0.4]	Low

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Alendronate—Effect modification of long-term efficacy

- Efficacy vs. placebo on risk of incident Fx varied by baseline BMD:

Population	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Osteoporosis	CF	0.64 [0.50, 0.82]	-7 [-10, -3]	Mod
	RVF	0.50 [0.31, 0.82]	-3 [-5, -1]	Mod
Osteopenia *T -2.5 to -2*	CF	1.03 [0.77, 1.39]	0.4 [-3, 4]	Low
	RVF	0.54 [0.28, 1.04]	-2 [-3, 0]	Low
Osteopenia *T -2 to -1.6*	CF	1.14 [0.82, 1.60]	1 [-2, 5]	Low
	RVF	0.82 [0.33, 2.07]	-0.2 [-2, 1]	Insuf

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Alendronate—Effect modification of long-term efficacy

- In women with osteoporosis, no eligible trials of long-term alendronate reported whether Fx efficacy varied by patient, bone or treatment characteristics.
- In women with osteopenia, efficacy vs. placebo on risk of incident Fx did not vary by:
  - Past NVF
  - Baseline FRAX MOF* score
  - Baseline bone turnover markers

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Zoledronate—Long-term efficacy

- 6-yr RCT (n=2000), PM women ≥65 yr, osteopenia by hip BMD (8% with T-score <-2.5 at spine or 1 hip; 13% had baseline RVF)

Population	Fx Outcomes†	HR [95% CI]	ARR [95% CI]	SOE
Osteopenia/ osteoporosis	CF	0.73 [0.60, 0.90]	-5 [-9, -2]	Low
	NVF	0.66 [0.51, 0.85]	-5 [-8, -2]	Mod
	CVF	0.41 [0.22, 0.75]	-2 [-3, -1]	Mod
	Hip Fx	0.66 [0.27, 1.16]	-0.4 [-1, 0.5]	Low

†Primary study outcome: incident "fragility Fx," defined as RVF or any NVF, excluding skull, face, mandible, toes, metatarsals, fingers, or metacarpals.

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Zoledronate—Effect modification of long-term efficacy

- Relative reduction in risk of fragility Fx similar to overall population after excluding:
  - Baseline RVF
  - Baseline BMD T-score < -2.5
- Relative reduction in risk of NVF, fragility Fx similar to overall population after excluding:
  - FRAX Hip Fx >3% or MOF >20% plus NVF since age 45

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Raloxifene—Long-term efficacy

- 4-yr RCT (n=7705) with 4-yr extension (n=4011), PM women, osteoporosis by BMD and/or past RVF

Population	Yr	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Osteoporosis	4	CVF	0.58 [0.43, 0.79]	-2 [-3, -1]	High
		RVF	0.64 [0.53, 0.76]	-5 [-6, -3]	High
		NVF	0.93 [0.81, 1.06]	No data	High
		Hip Fx	0.97 [0.62, 1.52]	No data	Mod
	8	NVF	1.00 [0.82, 1.21]	No data	Mod

- Efficacy vs. placebo for risk of incident Fx did not vary by age, baseline BMD or RVF

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Estrogen—Long-term efficacy

- 7-yr RCT (n=10,739), PM women 50-79 yr, unselected by Fx history or BMD (measured in 9%), no vertebral x-rays, s/p hysterectomy, compared CEE 0.625 mg PO daily vs. placebo

Population	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Overall	CF	0.71 [0.64, 0.80]	-4 [-5, -3]	High
	Hip Fx	0.65 [0.45, 0.94]	-0.5 [-0.9, -0.1]	Mod
	CVF	0.64 [0.44, 0.93]	-0.5 [-0.8, -0.1]	Mod
Past Fx (n=3816)	CF	0.73 [0.62, 0.86]	-5 [-7, -2]	Low
	Hip Fx	0.55 [0.32, 0.94]	-1 [-2, 0]	Low
Osteoporosis (n=53)	CF	0.83 [0.17, 3.91]	No data	Insuf
Osteopenia (n=363)	CF	0.83 [0.49, 1.40]	No data	Insuf

Estrogen/Progestin—Long-term efficacy

- 5.6-yr RCT (n=16,608), PM women 50-79 yr, unselected by Fx history or BMD (measured in 6%), no vertebral x-rays, intact uterus, compared CEE 0.625 mg + MPE 1.25 mg PO daily vs. placebo

Population	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Overall	CF	0.76 [0.69, 0.83]	-2 [-3, -1.5]	High
	Hip Fx	0.67 [0.47, 0.96]	-0.3 [-0.6, 0]	Mod
	CVF	0.65 [0.46, 0.92]	-0.3 [-0.5, -0.02]	Mod
Past Fx (n=5897)	CF	0.78 [0.68, 0.91]	-3 [-5, -1]	Low
	Hip Fx	0.77 [0.48, 1.22]	-0.3 [-0.9, 0.2]	Low
Osteoporosis (n~50)	CF	0.53 [0.25, 1.10]	No data	Insuf

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Estrogen and Estrogen/Progestin—Effect modification of long-term efficacy

- In women unselected for osteoporosis or osteopenia, efficacy vs. placebo on risk of incident hip or any clinical Fx (CF) did not consistently vary by any patient or bone characteristics

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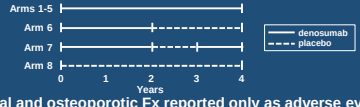
Denosumab

- 4-yr phase 2 RCT (n=365), PM women, osteoporosis or osteopenia by BMD



- Clinical and osteoporotic Fx reported only as adverse events.
- Unable to directly compare Fx risk or harms for continuous denosumab vs. placebo, drug holiday vs. placebo, or continuous vs. drug holiday, because only pooled results reported
  - Risk of SAE pooled denosumab vs. placebo: RR 1.6 [0.7, 3.9]

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Alendronate—Subtrochanteric/Femoral Shaft Fx without AFF Features

- No eligible alendronate studies with evidence on confirmed AFF

Control	Yr	Study Design	Population	HR [95%CI]	ARR [95%CI]	SOE
ST/FS FX WITHOUT CONFIRMED RADIOLOGIC AFF FEATURES						
Pbo	3-4.5	RCT (6459)	Osteoporosis or osteopenia	1.0 [0.1, 16.5]	0 [-0.1, 0.1]	Insuf
No ODT	3.8	Obs RC (534)	National database; ≥60y w nonhip Fx	1.4 [0.2, 8.6]	No data	Insuf
	≤6	Obs RC (220K)	National database ODT users/controls, ≥55y	ST: 2.4 [1.8, 3.3] FS: 2.9 [2.0, 4.3]	0.1 [0.08, 0.15] 0.09 [0.06, 0.12]	Low Low

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Alendronate—ONJ

Control	Yr	Study Design	Population	HR [95%CI]	ARR [95%CI]	SOE
RADIOLOGICALLY AND PATHOLOGICALLY CONFIRMED ONJ						
Raloxifene	~4	Obs (8354)	1 hospital database ODT users/controls, ≥50y	7.4 [1.0, 54.1]	No data	Insuf
DIAGNOSTIC CODES ONLY						
No ODT	3.8	Obs (534)	National database; ≥60y w nonhip Fx	3.2 [1.4, 6.9]	No data	Low
Raloxifene or Calcitonin	≤6	Obs (43,645)	National database; ≥50y, past hip or CVF, now on ODT	0.9 [0.4, 1.7]*	No data	Insuf

*Event rates reported by authors suggest HR possibly should be >1.

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Zoledronate—Long-term harms

Population	Design	Control	Yr	Harm	OR [95%CI]	ARR [95%CI]	SOE
PM women, osteopenia or osteoporosis by BMD	RCT (2000)	Pbo	6y	SAE	0.8 [0.7, 1.0]	-4 [-9, 0]	Low
				Vascular*	0.8 [0.5, 1.1]	-2 [-4, 0.5]	NG
				Mortality	0.7 [0.4, 1.1]	-1 [-3, 0.2]	NG
				Cancer†	0.7 [0.5, 0.9]	-4 [-6, -1]	NG
				AFF	0 [no events]	0 [no events]	Insuf
				ONJ	0 [no events]	0 [no events]	Insuf
				AFib	1.0 [0.7, 1.4]	0 [-2, 2]	NG

*Included sudden death, myocardial infarction, stroke, coronary artery revascularization.
†Excluded nonmelanoma skin cancers.

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Bisphosphonates—Atypical Femoral Fractures

Control	Yr	Design (cases)	Population	RR/OR [95%CI]	ARR [95%CI]	SOE
AFF WITH CONFIRMED RADIOLOGIC FEATURES						
No BP	≥3	Obs RC & CC (172)	National data; ≥55y	RC ≥4y: 126 [55, 238] CC 3-4y: 40 [17,91] CC 4-5y: 116 [58, 234] CC >5y: 93 [66, 132]	No data	Low
Past BP (none in ≥6m-5y)	≥5	Obs CC (43)	1 hospital data; ≥1y past BP use	3.4 [1.8, 11.9] to 5.2 [2.0, 13.4]	No data	Low

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Bisphosphonates—Subtrochanteric/Femoral Shaft Fx without AFF Features

Control	Yr	Design (cases)	Population	RR/OR/HR [95%CI]	ARR [95%CI]	SOE
ST/FS FX WITHOUT CONFIRMED RADIOLOGIC AFF FEATURES						
No BP	>3	Obs CC (44)	National data; ≥65y; nonhip Fx control	9.5 [2.2, 41.3]	10 [0, 20]	Low
Past BP (<100d)	≥3	Obs CC (325)	Provincial data; ≥68y; no ST/FS Fx control	3-5y: 1.6 [0.8, 3.2] ≥5y: 2.7 [1.3, 6.0]	3-5y: -1 [-5, 2] ≥5y: 4 [1, 7]	Low Low
Raloxif or Calciton	≥3	Obs RC (34)	Medicare data; non-ST/FS Fx control not specified	3-5y: 1.2 [0.6, 2.6] ≥5y: 2.0 [0.4, 10.0]	3-5y: 0.1 [-0,3, 0.5] ≥5y: 0.1 [-0.1, 0.4]	Insuf Insuf

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Raloxifene—Long-term harms

Population	Design	Control	Yr	Harms	RR/OR/HR [95%CI]	ARR [95%CI]	SOE
PM women, osteoporosis by BMD/RVF	RCT (4011)	Pbo	8	SAE	0.9 [0.9, 1.0]	-3 [-6, 0]	Mod
	RCT (7705 & 4011)	Pbo	4 & 8	DVT	2.8 [1.3, 5.9] to 3.1 [1.4, 6.9]	0.6 [0.2, 0.9] To 0.6 [0.3, 0.9]	NG
National database	Obs RC (19,324)	No ODT	3.8	ST Fx*	1.1 [0.3, 3.3]	0.04 [-0.06, 0.1]	Insuf
				FS Fx*	0.8 [0.2, 3.2]	0.01 [-0.07, 0.09]	
				ONJ*	0 [2 events]	0 [2 events]	Insuf
				AFib	0.8 [0.6, 1.1]	-0.02 [-0.4, 0.3]	NG

*Defined by diagnosis codes only

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Estrogen—Long-term harms

Population	Design (n)	Control	Yr	Harm	HR [95%CI]	SOE
PM women, hysterectomy	RCT (10,739)	Pbo	7	Global index*	NR	NG
-High Fx risk tertile					1.04 [0.88, 1.23]	NG
-Mid Fx risk tertile					1.09 [0.92, 1.30]	NG
-Low Fx risk tertile					0.81 [0.62, 1.05]	NG

*We did not systematically search for harms of long-term estrogen or estrogen/progestin beyond the global index measure.

†Global index defined as time to first of coronary heart disease, invasive breast cancer, stroke, pulmonary embolus, colorectal cancer, hip Fx, or death.

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Estrogen/Progestin—Long-term harms

Population	Design (n)	Control	Yr	Harm*	HR [95%CI]	SOE
PM women, intact uterus	RCT (16,608)	Pbo	5.6	Global index†	NR	NG
-High Fx risk tertile					1.03 [0.88, 1.24]	NG
-Mid Fx risk tertile					1.23 [1.04, 1.46]	NG
-Low Fx risk tertile					1.20 [0.93, 1.58]	NG

*We did not systematically search for harms of long-term estrogen or estrogen/progestin beyond the global index measure.

†Global index defined as time to first of coronary heart disease, invasive breast cancer, stroke, pulmonary embolus, colorectal cancer, hip Fx, or death.

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Long-term ODT harms—Effect modification

- Any bisphosphonate vs. control
  - Results from multiple observational studies suggest increased risk ST/FS Fx with longer treatment duration (>5y vs. 3-5 y)
- Estrogen or estrogen/progestin vs. placebo
  - Risk for global index similar across tertiles of Fx risk scale

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Alendronate—Drug holiday Fx effects

- Two RCTs (n=1449), PM women, past alendronate for osteopenia/osteoporosis by BMD

Pre-holiday population	Pre-holiday ODT	ODT Rx compare (n)	Fx Outcomes	HR [95% CI]	ARR [95% CI]	SOE
Osteoporosis *T ≤ -2.5*	ALN 5 y	ALN 2 y vs. PBO (350)	NVF CVF	0.87 [0.40, 1.91] 0.92 [0.40, 2.10]	-1 [-7, 5] -1 [-6, 5]	Low Low
	ALN 7 y	ALN 3 y vs. PBO (247)	NVF	0.81 [0.38, 1.71]	-2 [-11, 6]	Insuf
Osteopenia/ osteoporosis *T < -1.6*	ALN 5 y	ALN 5 y vs. PBO (1099)	CF NVF Hip RVF	0.93 [0.71, 1.21] 1.00 [0.76, 1.32] 1.02 [0.51, 2.10] 0.86 [0.60, 1.22]	-1 [-6, 4] -0.1 [-5, 5] 0 [-2, 2] -1 [-5, 2]	Mod Mod Low Low
			CVF	0.45 [0.24, 0.85]	-3 [-5, 0]	Mod

In women with past alendronate x 5 yr for osteoporosis or osteopenia, risk of incident Fx (NVF, CVF, RVF) with 5 more yr alendronate vs. placebo did not vary by pre-holiday RVF or BMD. [43]

Zoledronate—Drug holiday Fx effects

- Two RCTs (n=1449), PM women, past alendronate either for osteopenia or for osteoporosis by BMD/RVF

Pre-holiday population	Pre-holiday ODT	ODT Rx compare (n)	Fx Outcomes	HR/OR [95% CI]	ARR [95% CI]	SOE
Osteopenia *T <-1 & > -2.5*	ZA 1y	ZA 1y vs. PBO (379)	CF	1.37 [0.39, 4.78]	1 [-2, 4]	Insuf
Osteoporosis *T ≤-2.5 or T ≤-1.5 + RVF*	ZA 3y	ZA 3y vs. PBO (1233)	CF NVF Hip CVF	1.04 [0.71, 1.54] 0.99 [0.7, 1.5] 0.90 [0.33, 2.49] 1.81 [0.53, 6.2]	No data -0.3 [-3, 3] -0.2 [-1, 1] No data	Low Low Insuf Insuf
			RVF	0.51 [0.26, 0.95]	-3 [-6, -1]	Mod
	ZA 6y	ZA 3y vs. PBO (190)	CF RVF	1.11 [0.45, 2.73] 0.58 [0.13, 2.55]	1 [-7, 10] -2 [-8, 4]	Insuf Insuf

No evidence about whether differences in risk of Fx between zoledronate continuation vs. drug holiday vary by patient, bone or drug characteristics. [44]

Alendronate—Drug holiday harms

Population	Rx comparison	Design (n)	Harm	RR/OR/HR [95%CI]	ARR [95%CI]	SOE
Osteopenia/ osteoporosis, past ALN x 5y	ALN 5 y vs. PBO	RCT (1099)	SAE	No sign diff, but no data	No data	Insuf
			ST/FS Fx*	1.3 [0.1, 14.7]	-0.1 [-0.5, 0.7]	Insuf
			ONJ	No cases	No cases	Insuf
Osteoporosis, past ALN x 5y	ALN 2 y vs. PBO	RCT (350)	SAE	1.1 [0.6, 2.0]	1 [-7, 8]	Low
Osteoporosis, past ALN x 7y	ALN 3 y vs. PBO	RCT (247)	SAE	1.2 [0.8, 2.0]	5 [-7, 16]	Insuf

*Defined by diagnosis codes only.

- No evidence about whether differences in risk of harms between alendronate continuation and drug holiday vary by patient, bone or drug characteristics. [45]

Zoledronate—Drug holiday harms

Population	Rx compare	Design	Harm	RR/OR/HR [95%CI]	ARR [95%CI]	SOE
Osteopenia w past ZA x 1y	ZA 1y vs. PBO	RCT (379)	SAE	"No diff" (no data)		Insuf
			ONJ	0 [No cases]		Insuf
			Afib	0 [No cases]		NG
Osteoporosis w past ZA x 3y	ZA 3y vs. PBO	RCT (1233)	SAE	1.1 [1.0, 1.4]	4 [-1, 9]	Mod
			AFF	0 [No cases]		Insuf
			ONJ	0 [1 case]		Insuf
			AFib	3% vs. 2%, p=0.17	1.3 [-1, 3]	NG
Osteoporosis w past ZA x 6y	ZA 3y vs. PBO	RCT (190)	SAE	0.9 [0.5, 1.4]	-3 [-16, 9]	Low
			AFF, ONJ	0 [No cases]		Insuf
			AFib	5% vs. 1%, p=0.11	4 [-1, 9]	NG

- No evidence about whether differences in risk of harms between zoledronate continuation and drug holiday vary by patient, bone or drug characteristics.

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Limitations of Evidence

- All trials in healthy, largely white, PM women, and observational studies nearly all women; generalizability to other populations unknown
- Few trials on Fx efficacy of long-term ODT or ODT holidays
  - 1 trial each for most treatment comparisons
  - 2 trials with incident Fx as primary outcome (none for ODT holiday)
  - Few incident Fx events, especially hip Fx
- No data on efficacy or harms of long-term treatment with several individual agents, sequential ODT, or of different durations of ODT holidays

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Limitations of Evidence

- Variable definitions of AFF, ST/FS Fx & ONJ cases
- Observational studies variable for noncase controls, ODT treatment, treatment control, adjustment for osteoporosis status or other selection bias
- Data on possible effect modifiers limited and mostly post-hoc, at risk for type 1 errors

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Future Research Recommendations

- Future studies of long-term ODTs and ODT holidays should:
  - RCTs are the methodologically most rigorous design
  - Powered to assess clinical Fx endpoints, including hip Fx
  - Evaluate additional individual agents (e.g., risedronate, ibandronate, lower dose and transdermal hormone therapy, hormone therapy/SERM) and sequential therapy (e.g., anabolic followed by anti-resorptive)
  - Compare different durations of ODT holidays, with or without restarting ODT, including a continuous ODT comparison group
  - Include men, nonwhites, individuals with comorbidities
  - Include populations who meet neither BMD nor baseline RVF criteria for osteoporosis, but are at high Fx risk
  - Systematically collect and report harms data, using standard definitions for AFF and ONJ
  - Specify possible effect modifiers to examine a priori
  - Cohort studies on risk for AFF & ONJ should use standard definitions for cases, noncases, and exposure controls, and adequately adjust for BMD/osteoporosis status and selection bias

Future Research Recommendations

- Analyses of completed ODT trials:
  - Pooled patient-level data from multiple RCTs examining association of on-treatment changes in BMD and bone turnover markers with risk of incident clinical Fx may help determine whether these are appropriate surrogates.

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