The Salty Side of Supplements: Optimizing Supplement Selection

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OPA Annual Conference & Trade Show
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Ohio Pharmacists Association

1 VOICE VISION TEAM

Learning Objectives

1. Define commonly used terms to describe supplements
2. Compare commonly recommended supplements and their different formulations
3. Outline a framework for advising patients on supplement recommendations

Disclosure Statement

I have financial disclosures or conflicts of interest with the presented material in this presentation.

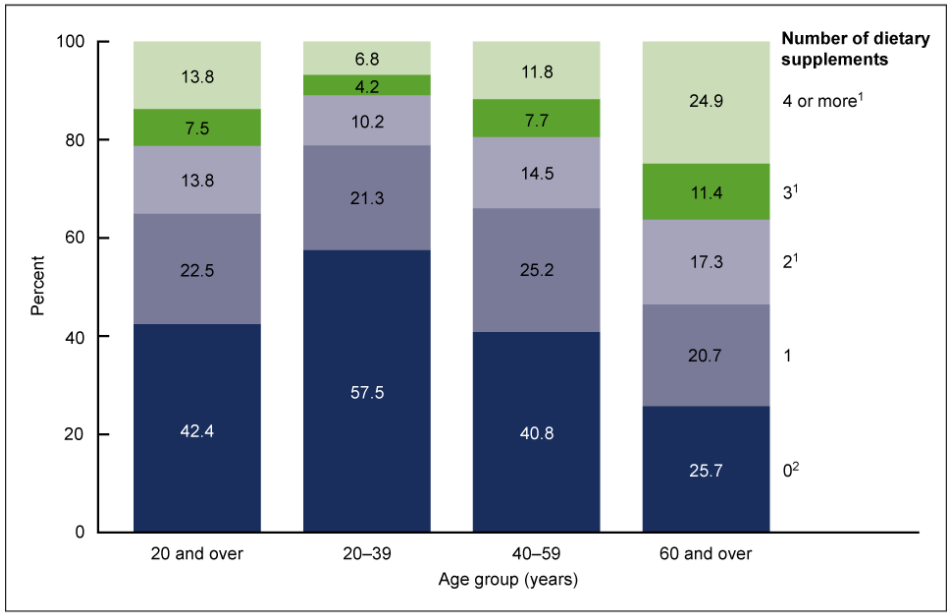
Owner - Emlah Naturals (A third-party tested dietary supplements company with a focus on education)

Why Do We Care?

In 2017-2018:

- 57.6% of US adults used a dietary supplement in the past 30 days
- 24.9% of adults >60 years of age report taking 4 or more supplements

Figure 2. Number of dietary supplements used by adults aged 20 and over, by age: United States, 2017–2018



[1]Significant linear increasing trend with age.
[2]Significant linear decreasing trend with age.
NOTE: Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db399-tables-508.pdf#2.
SOURCE: National Center for Health Statistics, National Health and Nutrition Examination Survey, 2017–2018.

https://www.cdc.gov/nchs/products/databriefs/db399.htm#:~:text=%2C%202017%E2%80%932018.-,Summary,supplements%20increased%20with%20increasing%20age

Mishra S, Stierman B, Gahche JJ, Potischman N. Dietary Supplement Use Among Adults: United States, 2017-2018. NCHS Data Brief. 2021 Feb;(399):1-8. PMID: 33663653.

Definitions

Salt forms = a salt is an electrically neutral chemical compound consisting of cations and anions connected by an ionic bond

The specific salts of active pharmaceutical ingredients (APIs) are often formed to achieve desirable formulation properties such as:

- Improve aqueous solubility
- Improve stability
- Improve absorption
- Decrease toxicity
- Economic considerations

Examples

- Acetate
- Carbonate
- Chloride
- Gluconate
- Maleate
- Stearate

Gupta D, Bhatia D, Dave V, Sutariya V, Varghese Gupta S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations. Molecules. 2018 Jul 14;23(7):1719. doi: 10.3390/molecules23071719. PMID: 30011904; PMCID: PMC6100526.

Definitions

Absorption = The transportation of the unmetabolized drug from the site of administration to the body circulation system

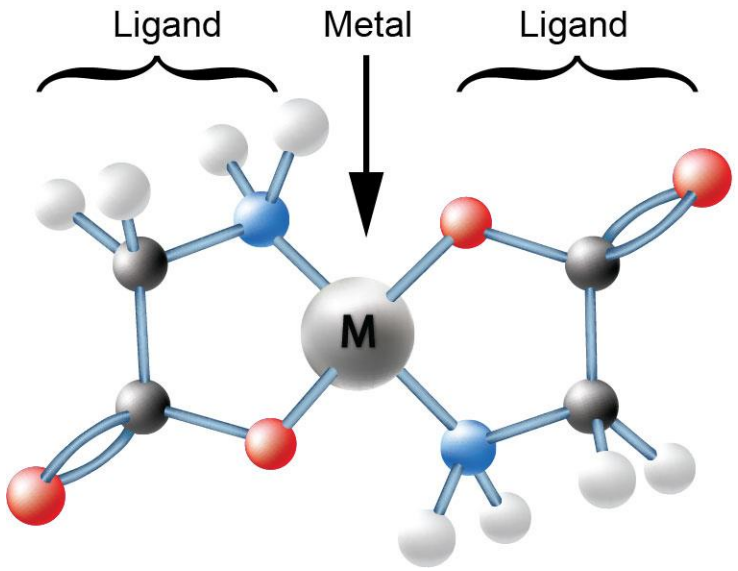
Bioavailability = The fraction of a dose of drug that successfully reaches the bodily fluid and is available to be used by the drug's intended target

Gupta D, Bhatia D, Dave V, Sutariya V, Varghese Gupta S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations. Molecules. 2018 Jul 14;23(7):1719. doi: 10.3390/molecules23071719. PMID: 30011904; PMCID: PMC6100526.

Definitions

Chelated = a compound containing a ligand (typically organic) bonded to a central metal atom at two or more points

- Chelated minerals are bound to compounds like amino or organic acids, which helps with absorption (improves bioavailability)



https://balchem.com/plant-nutrition/bioavailability-and-the-structure-of-chelated-minerals/

Gupta D, Bhatia D, Dave V, Sutariya V, Varghese Gupta S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations. Molecules. 2018 Jul 14;23(7):1719. doi: 10.3390/molecules23071719. PMID: 30011904; PMCID: PMC6100526.

Supplements

Calcium

Iron

Magnesium

What we will consider when talking about these different supplements:

- Forms
- Bioavailability/Absorption considerations
- Other considerations: Side effects, cost, availability

CALCIUM

Approximately 22% of men, 32% of women, and 4% to 8% of children take a dietary supplement containing calcium.

U.S. Department of Health and Human Services. (n.d.). *Office of dietary supplements - calcium*. NIH Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#:~:text=Approximately%2022%25%20of%20men%2C%2032,mg%20for%20children%20%5B18%5D.

Calcium

Food sources:

- Yogurt
- Milk
- Tofu
- White beans
- Kale
- Spinach
- Oranges

https://www.health.harvard.edu/blog/dairy-health-food-or-health-risk-2019012515849

Absorption from food = ~30%

Guilliams, T. G. (2014). *Supplementing dietary nutrients: A guide for healthcare professionals*. Point Institute.

Calcium - Forms

Salt Form	Percent Elemental Calcium
Calcium carbonate	36%
Calcium orotate	11%
Calcium citrate	24%
Calcium citrate malate	20%
Calcium ascorbate	9%
Calcium aspartate	20%
Calcium hydroxyapatite	37%
Tricalcium phosphate	34%
Calcium lactate	18%
Dicalcium matale	29%
Calcium amino acid chelates (bisglycinate)	18%

Guilliams, T. G. (2014). Supplementing dietary nutrients: A guide for healthcare professionals. Point Institute.

Calcium

Bioavailability/Absorption:

Varying data published

	Findings	Year of publication
Calcium carbonate versus calcium citrate	• Insignificant difference in absorption • Calcium carbonate significantly cheaper • Less tablets per dose consumed for calcium carbonate	2001
Calcium lysinate versus calcium carbonate	• Calcium lysinate was superior in absorption	2018

Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr. 2001 Jun;20(3):239-46. doi: 10.1080/07315724.2001.10719038. PMID: 11444420.

Shankar K, M S, Raizada P, Jain R. A Randomized Open-Label Clinical Study Comparing the Efficacy, Safety, and Bioavailability of Calcium Lysinate with Calcium Carbonate and Calcium Citrate Malate in Osteopenia Patients. J Orthop Case Rep. 2018 Jul-Aug;8(4):15-19. doi: 10.13107/jocr.2250-0685.1138. PMID: 30687654; PMCID: PMC6343570.

Calcium

Bioavailability/Absorption:

- Amino acid chelate calcium (calcium bisglycinate)
  - Removes barrier of calcium binding protein dependent absorption
  - Amino acid surrounds calcium ions and are completely absorbed (do not dissociate immediately after entering the bloodstream therefore increase absorption)
  - Cause less gastric upset than inorganic minerals

Zhang M, Liu K. Calcium supplements and structure-activity relationship of peptide-calcium chelates: a review. Food Sci Biotechnol. 2022 Jul 16;31(9):1111-1122. doi: 10.1007/s10068-022-01128-6. PMID: 35919358; PMCID: PMC9339050.

https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/

Calcium - Considerations

What to consider when recommending calcium?

- Maximum 500mg/dose - key counseling point
- Tablet burden
- Cost
- Indication

Calcium Summary

- Chelated forms of calcium have improved bioavailability and absorption over other salt forms of calcium.
- Calcium supplement salt forms vary in cost.
- The maximum calcium per dose should be 500mg for optimal absorption of any formulation of calcium.

IRON

Approximately 14% to 18% of Americans use a supplement containing iron.

U.S. Department of Health and Human Services. (n.d.-b). Office of dietary supplements - iron. NIH Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/

Iron

Food sources:

- **Heme Iron**
  - Animal flesh
    - Red meat, fish, poultry
  - More bioavailable than non-heme
  - High intake associated with cancer, diabetes and cardiovascular diseases.

Food sources:

- **Non-heme Iron**
  - Vegetables/Plants/Dairy
    - Beans
    - Grains
    - Dark leafy greens
    - Vegetables
  - Less bioavailable

Hooda J, Shah A, Zhang L. Heme, an essential nutrient from dietary proteins, critically impacts diverse physiological and pathological processes. Nutrients. 2014 Mar 13;6(3):1080-102. doi: 10.3390/nu6031080. PMID: 24633395; PMCID: PMC3967179.

Iron - Forms

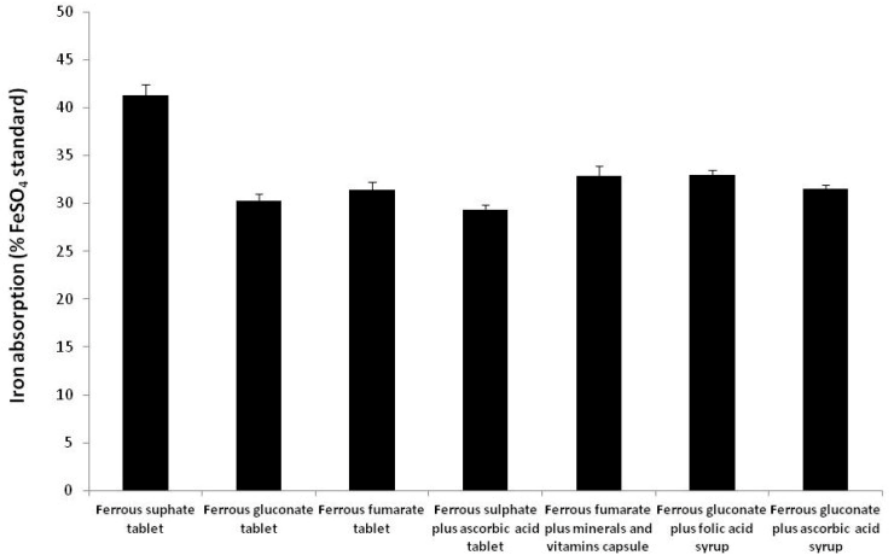
Salt Form	Percent Elemental Iron
Ferrous fumarate	33%
Ferrous sulfate (monohydrate)	33%
Ferrous sulfate (heptahydrate)	22%
Ferrous gluconate	12%
Ferrous oxide	77%
Ferrous amino acid chelates (bisglycinate)	18%

Guilliams, T. G. (2014). Supplementing dietary nutrients: A guide for healthcare professionals. Point Institute.

Iron

Bioavailability/Absorption:

- Heme (ferrous) iron is better absorbed than non-heme (ferric) iron.
  - Ferric iron bioavailability is typically 3 to 4 times lower than that of ferrous sulfate.



Zariwala MG, Somavarapu S, Farnaud S, Renshaw D. Comparison study of oral iron preparations using a human intestinal model. Sci Pharm. 2013 Jun 21;81(4):1123-39. doi: 10.3797/scipharm.1304-03. PMID: 24482777; PMCID: PMC3867244.

Iron

Bioavailability/Absorption:

- **Ferrous fumarate**
  - Lower toxicity profile because of low solubility and slow dissolution rate
  - Rate of release of ferrous ions from ferrous fumarate is slower

Zariwala MG, Somavarapu S, Farnaud S, Renshaw D. Comparison study of oral iron preparations using a human intestinal model. Sci Pharm. 2013 Jun 21;81(4):1123-39. doi: 10.3797/scipharm.1304-03. PMID: 24482777; PMCID: PMC3867244.

Iron

Bioavailability/Absorption:

- **Ferrous bisglycinate**
  - Demonstrated to have at least 2 folder higher bioavailability and absorption compared to conventional salts (sulfate and fumarate)
  - Improved oral tolerability
    - Head to head study demonstrated less side effects compared to ferrous fumarate

Coplin M, Schuette S, Leichtmann G, Lashner B. Tolerability of iron: a comparison of bis-glycino iron II and ferrous sulfate. Clin Ther. 1991 Sep-Oct;13(5):606-12. PMID: 1799918.

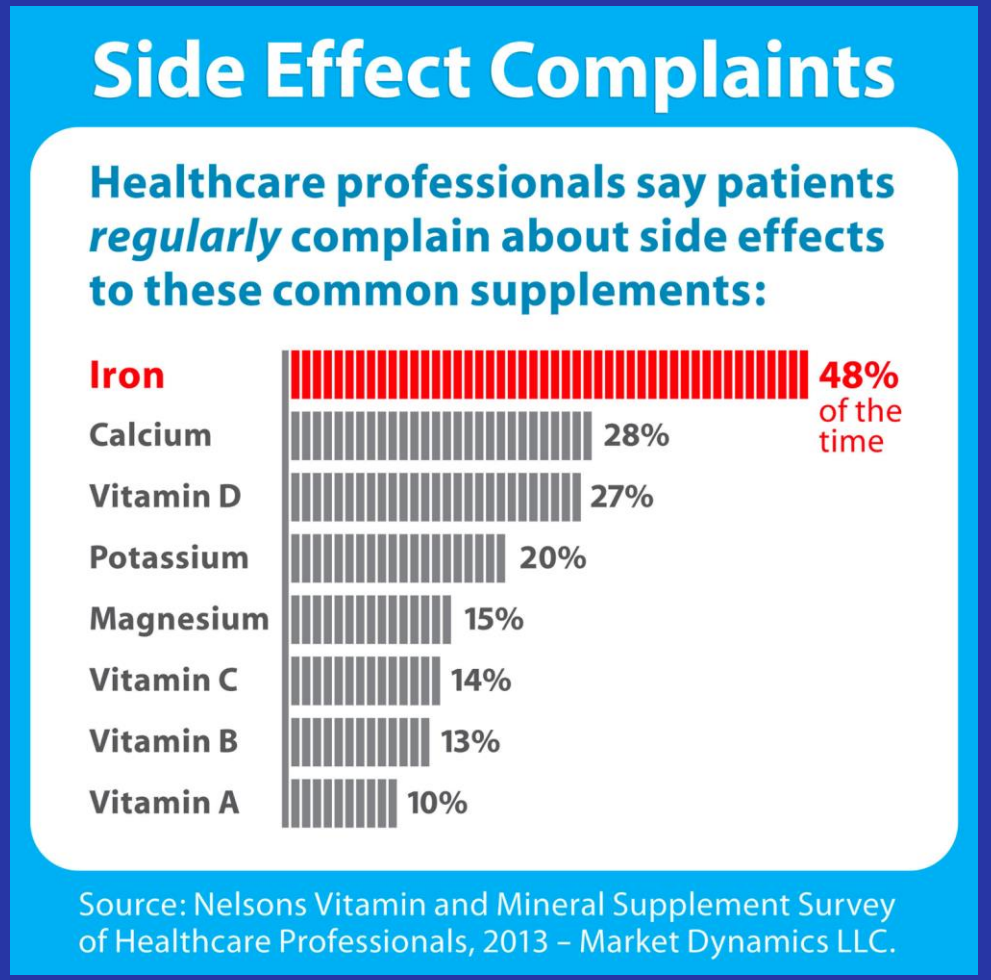
Iron

Bioavailability/Absorption:

- **Ferrous bisglycinate (continued)**
  - 2019 study conducted in pregnant women with second trimester iron deficiency anemia
    - Ferrous bisglycinate was more efficient in increasing hemoglobin levels and had fewer side effects compared to ferrous sulfate.

Abbas AM, Abdelbadee SA, Alanwar A, Mostafa S. Efficacy of ferrous bis-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. J Matern Fetal Neonatal Med. 2019 Dec;32(24):4139-4145. doi: 10.1080/14767058.2018.1482871. Epub 2018 Jun 20. PMID: 29843553.

Iron - Side Effects



Nelsons. (2018, June 30). Iron supplements lead in patient complaints. PR Newswire: press release distribution, targeting, monitoring and marketing. https://www.prnewswire.com/news-releases/iron-supplements-lead-in-patient-complaints-235398061.html

Iron - Considerations

What to consider when recommending iron?

- Iron overdose is the largest cause of poisoning fatalities in children less than 6 years old- key counseling point
- Common side effects: Nausea, constipation

Iron Summary

- Incorporating iron rich foods into the diet is important, but don’t overdo it on heme sources.
- Studies have shown effectiveness of ferrous bisglycinate in addition to higher compliance (do to less side effects) and low discontinuation rates compared to other formulations.

MAGNESIUM

48% of Americans of all ages ingest less magnesium from food and beverages than the estimated average requirement.

U.S. Department of Health and Human Services. (n.d.-c). Office of dietary supplements - magnesium. NIH Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/

Magnesium

Food sources:

- Almonds
- Cashews
- Peanuts
- Cooked spinach
- Black beans
- Soy beans
- Edamame

https://www.health.com/high-protein-vegetables-7551191

Guilliams, T. G. (2014). Supplementing dietary nutrients: A guide for healthcare professionals. Point Institute.

Magnesium - Forms

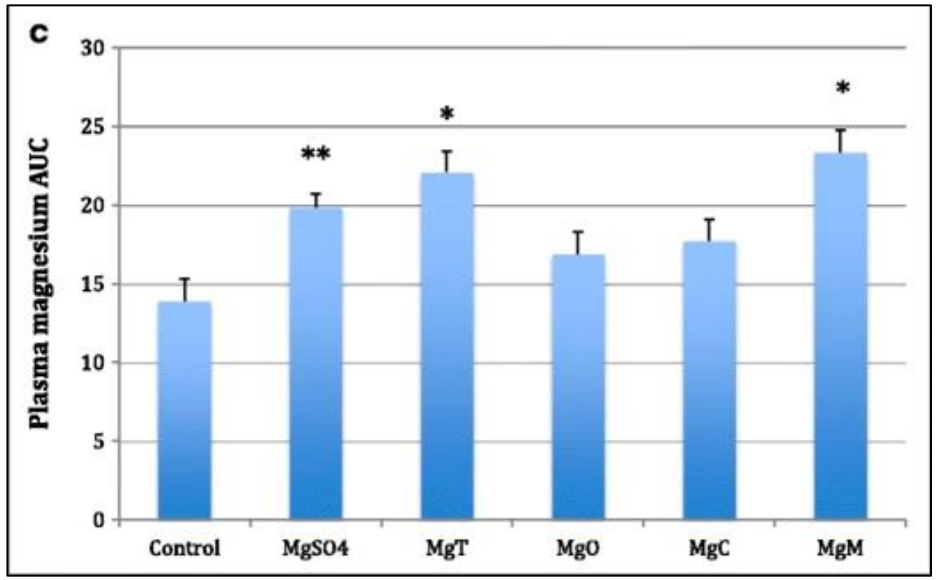
Salt Form	Percent Elemental Magnesium
Magnesium oxide	60%
Magnesium chloride	25%
Magnesium carbonate	25%
Magnesium citrate	16%
Magnesium ascorbate	18%
Magnesium lactate	12%
Magnesium aspartate	20%
Magnesium threonate	7%
Magnesium amino acid chelate (glycinate)	10%

Guilliams, T. G. (2014). Supplementing dietary nutrients: A guide for healthcare professionals. Point Institute.

Magnesium

Bioavailability/Absorption:

- Multiple studies have shown magnesium oxide, although high in magnesium content, has poor bioavailability compared to other forms of magnesium.



Uysal N, Kizildag S, Yuce Z, Guvendi G, Kandis S, Koc B, Karakilic A, Camsari UM, Ates M. Timeline (Bioavailability) of Magnesium Compounds in Hours: Which Magnesium Compound Works Best? Biol Trace Elem Res. 2019 Jan;187(1):128-136. doi: 10.1007/s12011-018-1351-9. Epub 2018 Apr 21. PMID: 29679349

Magnesium

Bioavailability/Absorption:

- **Magnesium amino acid chelate (glycinate, bisglycinate)**
  - The bonds between magnesium and amino acids are stronger, more stable, and survive longer in the bloodstream.
  - It protects magnesium from chemical reactions that may lead to unabsorbed precipitates**.**

Ates M, Kizildag S, Yuksel O, Hosgorler F, Yuce Z, Guvendi G, Kandis S, Karakilic A, Koc B, Uysal N. Dose-Dependent Absorption Profile of Different Magnesium Compounds. Biol Trace Elem Res. 2019 Dec;192(2):244-251. doi: 10.1007/s12011-019-01663-0. Epub 2019 Feb 13. PMID: 30761462.

Magnesium - Considerations

What to consider when recommending magnesium?

- Indication? Do you want laxative effect?
  - Example: magnesium citrate used for side effect of diarrhea
- Dosing schedule
  - Divided doses preferred for higher dosing

Magnesium Summary

- The most commonly prescribed forms of magnesium often have the lowest bioavailability.

- Choosing a chelated formulation in divided dose provides the best bioavailability and retention.

MAKING RECOMMENDATIONS

Making Recommendations

Questions to Ask:

- Why?
- Comorbidities? Side effect concerns?
- Tablet burden an issue?
- Is cost a factor?

Counseling:

- How to read labels
- Factors that impact absorption
  - How is the medication best taken?

Summary

Salt Forms Matter

- Millions of Americans take supplements and are interested in taking supplements.
- Salt form impacts the bioavailability and tolerability of supplements.

- The intent of chelated supplements is:
  - To make them more affordable
  - Improve bioavailability
  - Mitigate side effects

PUTTING IT ALL TOGETHER

Community Pharmacist Scenario

Allie - 32 years old and pregnant comes to the counter with:

- Magnesium citrate bottle
- Prenatal vitamin gummies (no iron)
- Ferrous bisglycinate
- Calcium citrate + vitamin D

Question 1 -

Which of the following questions would you ask Allie? (Select all that apply)

1. Why does she need magnesium?
2. What is the calcium citrate and vitamin D for?
3. Are there any side effects to consider regarding this supplement regimen?

Community Pharmacist Scenario

Allie - 32 years old and pregnant comes to the counter with:

- Magnesium citrate bottle
- Prenatal vitamin gummies (no iron)
- Ferrous bisglycinate
- Calcium citrate + vitamin D

Question 1 -

Which of the following questions would you ask Allie? (Select all that apply)

1. **Why does she need magnesium?**
2. **What is the calcium citrate and vitamin D for?**
3. **Are there any side effects to consider regarding this supplement regimen?**

Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
- Calcium citrate + vitamin D is for her mom with osteopenia
- Already experience constipation

Question 2 -

Which of the following is true?

1. Allie has all the right supplements and you should sell them to her
2. You should not sell the magnesium citrate for sleep
3. Magnesium bisglycinate may be a safe, well tolerated alternative for sleep

Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
- Calcium citrate + vitamin D is for her mom with osteopenia
- Already experience constipation

Question 2 -

Which of the following is true?

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Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
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Question 3 -

As it relates to constipation you should:

1. Reassure her that she has selected an iron formulation with the lowest side effect profile
2. Recommend she switch to ferrous sulfate
3. Recommend she switch to ferrous fumarate

Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
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Question 3 -

As it relates to constipation you should:

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Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
- Calcium citrate + vitamin D is for her mom with osteopenia
- Already experience constipation

Question 4 -

How would you recommend Allie's mom take the calcium citrate 500mg - vitamin D 400 IU per tablet

1. Take 2 tablets by mouth daily
2. Take 1 tablet by mouth twice daily
3. Take 2 tablet by mouth twice daily

Community Pharmacist Scenario

- Magnesium citrate bottle is for sleep
- Calcium citrate + vitamin D is for her mom with osteopenia
- Already experience constipation

Question 4 -

How would you recommend Allie's mom take the calcium citrate 500mg - vitamin D 400 IU per tablet

1. Take 2 tablets by mouth daily
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3. Take 2 tablet by mouth twice daily

References

1. https://www.cdc.gov/nchs/products/databriefs/db399.htm#:~:text=%2C%202017%E2%80%932018.-,Summary,supplements%20increased%20with%20increasing%20age
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4. U.S. DU.S. Department of Health and Human Services. (n.d.). *Office of dietary supplements - calcium*. NIH Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#:~:text=Approximately%2022%25%20of%20men%2C%2032,mg%20for%20children%20%5B18%5Department of Health and Human Services. (n.d.). *Office of dietary supplements - calcium*. NIH Office of Dietary Supplements.
5. Guilliams, T. G. (2014). *Supplementing dietary nutrients: A guide for healthcare professionals*. Point Institute.
6. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#:~:text=Approximately%2022%25%20of%20men%2C%2032,mg%20for%20children%20%5B18%5D.
7. Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr. 2001 Jun;20(3):239-46. doi: 10.1080/07315724.2001.10719038. PMID: 11444420.
8. Shankar K, M S, Raizada P, Jain R. A Randomized Open-Label Clinical Study Comparing the Efficacy, Safety, and Bioavailability of Calcium Lysinate with Calcium Carbonate and Calcium Citrate Malate in Osteopenia Patients. J Orthop Case Rep. 2018 Jul-Aug;8(4):15-19. doi: 10.13107/jocr.2250-0685.1138. PMID: 30687654; PMCID: PMC6343570.
9. Zhang M, Liu K. Calcium supplements and structure-activity relationship of peptide-calcium chelates: a review. Food Sci Biotechnol. 2022 Jul 16;31(9):1111-1122. doi: 10.1007/s10068-022-01128-6. PMID: 35919358; PMCID: PMC9339050.
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References

11. Hooda J, Shah A, Zhang L. Heme, an essential nutrient from dietary proteins, critically impacts diverse physiological and pathological processes. Nutrients. 2014 Mar 13;6(3):1080-102. doi: 10.3390/nu6031080. PMID: 24633395; PMCID: PMC3967179.
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13. Zariwala MG, Somavarapu S, Farnaud S, Renshaw D. Comparison study of oral iron preparations using a human intestinal model. Sci Pharm. 2013 Jun 21;81(4):1123-39. doi: 10.3797/scipharm.1304-03. PMID: 24482777; PMCID: PMC3867244.
14. Coplin M, Schuette S, Leichtmann G, Lashner B. Tolerability of iron: a comparison of bis-glycino iron II and ferrous sulfate. Clin Ther. 1991 Sep-Oct;13(5):606-12. PMID: 1799918.
15. Abbas AM, Abdelbadee SA, Alanwar A, Mostafa S. Efficacy of ferrous *bis*-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. J Matern Fetal Neonatal Med. 2019 Dec;32(24):4139-4145. doi: 10.1080/14767058.2018.1482871. Epub 2018 Jun 20. PMID: 29843553.
16. Nelsons. (2018, June 30). *Iron supplements lead in patient complaints*. PR Newswire: press release distribution, targeting, monitoring and marketing. https://www.prnewswire.com/news-releases/iron-supplements-lead-in-patient-complaints-235398061.html
17. U.S. Department of Health and Human Services. (n.d.-c). *Office of dietary supplements - magnesium*. NIH Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/
18. Uysal N, Kizildag S, Yuce Z, Guvendi G, Kandis S, Koc B, Karakilic A, Camsari UM, Ates M. Timeline (Bioavailability) of Magnesium Compounds in Hours: Which Magnesium Compound Works Best? Biol Trace Elem Res. 2019 Jan;187(1):128-136. doi: 10.1007/s12011-018-1351-9. Epub 2018 Apr 21. PMID: 29679349.
19. Ates M, Kizildag S, Yuksel O, Hosgorler F, Yuce Z, Guvendi G, Kandis S, Karakilic A, Koc B, Uysal N. Dose-Dependent Absorption Profile of Different Magnesium Compounds. Biol Trace Elem Res. 2019 Dec;192(2):244-251. doi: 10.1007/s12011-019-01663-0. Epub 2019 Feb 13. PMID: 30761462.

Need More Information?

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