CHI Health

Medication Management

Deprescribing Medications that are No Longer of Benefit

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Deprescribing

Deprescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes.[1] In 2021, medication cost rose 7.7% compared to the year prior, with utilization (increased number of medications prescribed) being the primary driver over price increases.[2] Polypharmacy, defined as taking five or more chronic medications, is becoming more prominent as our population ages.[3] Increased life expectancy means more people are living with chronic conditions, requiring multiple medications to manage their health. For these patients, polypharmacy may be appropriate; however, the medications recommended in the management of one chronic health condition, may be contraindicated due to another health condition or an interaction with a medication used to manage another condition. One in three older adults may be taking an inappropriate medication and exposing themselves to health risks as well as unnecessary expense.[4] Polypharmacy is associated with increased risk of falls in the elderly, with the risk increasing with each additional pill regardless of the medication.[5] It is important to regularly review medication lists when evaluating a new complaint to ensure it is not a side effect of a medication the patient is taking. Determining the timing of symptom onset in relation to starting a new medication can help determine a medication cause and prevent costly work-up and mismanagement. Prescribing cascades (prescribing medications to manage a side effect of another medication) can easily occur if clinicians are not careful to consider a medication as the underlying etiology of a health complaint, with these cascades only serving to propagate polypharmacy.[6]

As rising medication costs outpace other medical costs and strain household budgets, it is important that prescribers regularly review medication regimens (including over the counter medications) to assess each medication's ongoing indication and effectiveness to ensure the benefit outweighs any risks associated with each medication. While prescribing a new medication is a relatively simple and often a well-received process, how and when to consider deprescribing can be more complicated. Physicians are often reluctant to discontinue medications, especially when they did not prescribe the medication and the patient is tolerating it. (see table 1) Patients may also be reluctant to discontinue medications fearing adverse impact on their health even in the absence of an ongoing indication (see table 2). However, 80% of older adults ages 50 to 80 would be open to stopping one or more of their prescribed medications, according to a 2023 poll by researchers at the University of Michigan.[7] Reassurance of close follow-up to assess for any negative impact can help relieve these fears and gain acceptance to the plan.

Table 1.
Provider-related barriers to deprescribing[8]

- Assumption that patient is not interested in deprescribing
- Fear of adverse drug withdrawal effects
- Fear of changing the status quo
- Difficulty with medication reconciliation (patient receiving medications from multiple providers, multiple pharmacies)
- Reassigning responsibility to another provider
- Pressure from clinical practice guidelines
- Lack of time (typical office visit may not offer adequate time for a deprescribing discussion)
- Lack of organizational support
- Concern that effective alternatives are not available
- Fear of consequences in quality measures
- Ambiguity regarding feasibility of deprescribing
- Unclear medication indication

Table 2.
Patient-related barriers to deprescribing[8]

- Fear of adverse drug withdrawal effects
- Fear of changing the "status quo"
- Disagreement with deprescribing reason
- Negative "influences" to deprescribing medication (eg, previously told they should take the medication "for the rest of their life," influence of family/caregivers/friends)
- Absence of a deprescribing process

Patients (and prescribers) may also have a lack of understanding regarding the safety risks and actual indications/benefits (especially OTC and supplements), leading to a reluctance to attempt deprescribing.

Clinical Pharmacists can be a helpful resource to optimize a patient's medication regimen to help identify cost savings as well as opportunities for deprescribing. CHI Health Partners have Clinical Pharmacists available for consultation by placing a referral in EPIC or by calling 402-717-7247.

Deprescribing Opportunities

Any chronic medication is a potential deprescribing opportunity if the indication no longer exists, the medication is responsible for a side effect, or the risk of the medication now outweighs any potential benefit. Some common medications to consider include:

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) have become some of the most commonly prescribed medications in the past decade. Their ability to shut off parietal cell H+/K+ ATPase was a significant advancement in the management of GERD and other acid related disorders. These medications are indicated for limited (8-12 week) courses for the majority of their indicated conditions but are frequently continued long term in patients who are asymptomatic or minimally symptomatic.

Acid inhibition by PPIs results in elevated gastrin levels which upon discontinuation of the medication can result in rebound gastric acid production and a return of symptoms. This feedback loop can make it difficult for patients to come off the medication. There is uncertainty in regards to the safety of long term PPI therapy. While causation has not been determined, long term PPI therapy has been associated with osteoporosis, vitamin deficiencies, increased risk of pulmonary infections, C. diff infections, kidney injury,and gastric cancer[9] as well as potential drug interactions with clopidogrel.[10]

In patients who experience rebound symptoms after discontinuation, gradual tapering of the dose over several weeks with the use of on-demand treatment with an H2-blocker or antacids for breakthrough symptoms can be effective in helping patients wean from these medications. AGA recommends that most patients on PPIs undergo regular review to determine if therapy is still necessary, with a trial of deprescribing in those without definitive indications. Patients on twice -daily dosing should attempt to step-down to once daily dosing. Routine deprescribing is not recommended in patients with erosive esophagitis, Barrett's, eosinophilic esophagitis, esophageal ulcerations or strictures or idiopathic pulmonary fibrosis.[11]

Proton Pump Inhibitor patient education

Pain Medications

There is a lack of evidence for the long-term effectiveness of opioids to relieve chronic pain.[12] Chronic opioid therapy has been associated with hyperalgesia, or state of nociceptive sensitization caused by exposure to opioids in which some patients become more sensitive to certain painful stimuli or their preexisting pain worsens.[13] This paradoxical response can be difficult to discern from actual exacerbation of underlying pain and may result in an inappropriate dose escalation. Given the lack of evidence for long-term benefit from chronic opioid use and the well known risks associated with these medications, it is reasonable to continually reassess the risk/benefits of continued use and encourage attempts at weaning. Recently guidelines have been published to help guide clinicians in deprescribing opioid pain medications.[14]

Opioid deprescribing guidelines

To begin weaning the dose, a decrease of 10% of the original dose in oral morphine equivalents (OME) each week was proposed as the default starting point. Slower tapers (e.g. 10% per month) is recommended as more appropriate and better tolerated for patients who had been taking high doses of opioids for many years.[15] Small reductions in doses initially may help to cultivate trust between prescriber and patient and minimize fears about withdrawals.[14] Withdrawal symptoms can be managed with clonidine 0.1 mg every 6 hours as needed, antiemetics

and anti-diarrheals. An alternative pain strategy should be agreed upon prior to weaning and may include NSAIDs, non-opioid pain medications, alternative pain medications (e.g. anti-epileptics, antidepressants), and/or cognitive behavioral training.

There has been increased concern about the potential risks (e.g. self-harm) from rapid discontinuation of chronic opioid therapy[14,16,18]. Successful weaning depends upon a trusting relationship between patient and prescriber. Health care professionals should consider the potential harms of deprescribing for people receiving high dose chronic opioid treatment and monitor specifically for suicidal thoughts.[14]

Once the dose is reduced, most patients can be expected to report their pain is no worse and their function and quality of life is improved, especially when an alternative approach to pain management is provided.[18]

Pocket Guide: Tapering Opioids for Chronic Pain

Gabinoids[19]

Recent years have seen a rapid increase in off-label prescribing for gabapentinoids (Lyrica/pregabalin, Neurontin/gabapentin) in part to generic versions of each being released over the past two decades, but also in response to calls for strategies to limit opioids for chronic pain management. Although this medication class has demonstrated high safety profiles there are still risks for abuse among patients with opioid addictions as well as falls with injury in elderly patients.[20] Currently, there is no consensus on the best method to deprescribe gabapentinoids, but limited studies suggest slow weaning especially in patients on high baseline dosages.[21] Side effects of deprescribing include insomnia, headaches and dizziness.[22]

Bisphosphonates

Bisphosphonates have been shown to increase bone mineral density and reduce the risk of hip and vertebral fractures in women with previous fractures. The new FDA recommendation, indicated in revised labeling, states that "the optimal duration of use has not been determined, however studies suggest that after 5 years of treatment, patients should be reassessed to determine if ongoing treatment is warranted.[23,24] Bisphosphonates have a prolonged half-life and studies have shown persistent effects after discontinuation.[25] Studies have suggested efficacy of prolonged bisphosphonate therapy in maintaining bone density for up to 10 years with alendronate, 7 years with risedronate, and 6 years with zoledronic acid (ZOL), but evidence regarding fracture risk reduction with longer therapy is less convincing.[26] **No clinical trials have investigated use beyond ten years.** Patients without previous fractures whose BMD T-score is > -2.5 could consider pausing the medication after 5-10 years of treatment. Patients with previous fractures or high-risk for osteoporotic fractures (a T-score below -3.0 in the absence of fractures) could continue treatment for an additional 5-years. Once the decision is made to discontinue treatment, patients should have a DEXA scan every 2-3 years to look for ongoing bone loss. Patients with >5% bone loss should consider resuming treatment. Treatment after 10 years is associated with increased risk of atypical femoral neck fractures. Atypical femoral fractures have been associated with bisphosphonate use despite treatment reducing the overall risk of fractures. These fractures may arise from small stress fractures in the lateral cortex of the femur that fail to heal, propagating to become complete transverse shaft fractures.(27) The FDA review noted that "there is no agreement on the extent to which cumulative use of bisphosphonates increases the risk" of atypical fractures.[26]

Aspirin

Meta-analyses of recent studies have resulted in changes to guidelines for prophylactic aspirin therapy. The USPSTF does not recommend aspirin for primary prophylaxis in patients over the age of 60. There appears to be a small benefit in patients ages 40-59 with a 10-year ASCVD risk of 10% or greater. In these patients, therapy should be individualized based on patient preference.[28] The American College of Cardiology/American Heart Association (ACC/AHA) states low dose aspirin should be infrequently used for primary prevention but may be considered in select patients, age 40-69, at higher CVD risk.[29] The American Diabetes Association (ADA) recommends that low-dose (75-162 mg/d) aspirin should be considered for prevention of ASCVD in adults older than 50 years with diabetes and at least 1 major ASCVD risk factor (see "a") and not at increased risk of bleeding (see "b")

(a) Major ASCVD Risk: Family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria.

(b) Bleeding risk: Taking concurrent medications that increase bleeding risk, history of gastrointestinal bleed, peptic ulcer disease, older age, anemia, or kidney disease. For patients older than 70 years with or without diabetes, the risk appears greater than the benefit.

All guidelines emphasize shared decision-making with consideration of cardiovascular benefit and cancer prevention vs increased risk of bleeding.

Up to a third of patients taking anticoagulants may also be taking aspirin without a clear indication and exposing themselves to an increased risk of bleeding. In patients without a history of coronary artery disease, myocardial infarction, any percutaneous coronary intervention, coronary artery bypass grafting, peripheral arterial disease, mechanical valve replacement, or use of left ventricular assist devices, it may be appropriate to stop aspirin/antiplatelet therapy while they are anticoagulated.[30]

Sleeping pills

Cognitive behavioral therapy for insomnia (CBT-I) is the preferred first-line treatment for chronic insomnia in adults and has been endorsed by multiple societies and guideline panels.[31] Most sleeping pills have indications for short-term (2-4 weeks) use, however many patients end up taking them on an ongoing basis. A recent network meta-analysis, identified 154 placebo-controlled randomized trials of 30 different medications for insomnia in nearly 45,000 participants, of which only five trials were longer than four weeks.[32] **The efficacy of benzodiazepine receptor agonists (BZRAs) for insomnia can be diminished in as little as 4 weeks.**[33] Use of BZRAs is associated with increased risk of falls, motor vehicle accidents, memory problems, and daytime sedation, especially in the elderly. There are many underlying reasons for insomnia and it may be difficult to determine an underlying etiology (depression, anxiety, drug or alcohol use, pain,cardiopulmonary disease, sleep apnea, nocturia, restless legs, menopause, medication side effects, among others) during the initial assessment. Ongoing efforts to identify and treat the underlying cause or determine if it has resolved on its own may allow deprescribing of the sleep aid.

A gradual taper over a few days to weeks may help prevent rebound insomnia. Benzodiazepine receptor agonists (e.g. zolpidem, alprazolam, temazepam) may need to be tapered over a longer period. Tapering BZRA sleep medications

Is a Benzodiazepine or Z-Drug still needed for sleep?

Sleep advice

1. Go to bed only when sleepy
2. Do not use bed or bedroom for anything but sleep (or intimacy)
3. If not asleep within about 20-30 min at the beginning of the night or after an awakening, exit the bedroom
4. If not asleep within 20-30 min on returning to bed, repeat #3
5. Use alarm to awaken at the same time every morning
6. Do not nap
7. Avoid caffeine after noon
8. Avoid rigorous exercise, nicotine, alcohol, and big meals within 2 hrs of bedtime
9. Exercise daily

Antidepressants

Guidelines recommend treatment with antidepressants for a minimum of 4-9 months to reduce the risk of relapse.[34] Ongoing maintenance therapy is appropriate for patients with certain risk factors for recurrent symptoms:[34,35]

- History of physical or sexual abuse, neglect, or family violence or conflict
- Residual depressive symptoms, especially sleep disturbances and/or suicidal ideation
- Previous episodes of major depression
- Early age of onset
- Comorbid anxiety disorders
- Family history of mood disorders Prominent depressive cognition, neuroticism or rumination
- Ongoing psychosocial stressors or impairment

In patients who have had a complete response and lack risk factors for recurrence, tapering of the medication could be considered. If pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. Before the discontinuation of active treatment, patients should be informed of the potential for a relapse and a plan should be established for resumption of treatment should this occur.[35]

Long-acting sulfonylureas

Sulfonylureas were the first oral medications for the treatment of type 2 diabetes. Their major mechanism of action is stimulating insulin secretion from pancreatic beta-cells. This secretion happens independent from blood glucose levels however and can result in profound hypoglycemia. There is also concern for increased risk for cardiovascular events and mortality in patients taking these medications. This was demonstrated with a first generation sulfonylurea which is no longer used.[36] The risk of hypoglycemia is amplified in patients with CKD.[37] Glyburide, due to its high renal excretion, is contraindicated in CKD-3 (eGFR<60 mL/min). Studies looking at 2nd generation sulfonylureas have been inconclusive.[38] Weight gain is a common side effect of these medications. Newer diabetic medications do not cause hypoglycemia nor contribute to beta-cell dysfunction and may help with weight loss making sulfonylureas less attractive today. Their cost, however, is a major benefit over many of the other diabetic medications.

Sulfonylureas have also exhibited a lack of durability. Several studies have shown progressive loss of glycemic control starting as early as 6 months after initiation of these medications. This lack of durability may be related to their mechanism of action contributing to hyperinsulinemia and escalating the beta cell dysfunction.[39] It may be reasonable to attempt discontinuation in patients who have been on a sulfonylurea for many years with other diabetic medications, as its glycemic effect may be minimal.

Daily NSAIDS

NSAIDs are some of the most commonly prescribed medications, and their availability over the counter further exposes patients to their potentially serious side effects. Studies have shown that these agents can worsen hypertension and increase the risk of both myocardial infarction (MI) and atrial fibrillation, with some studies indicating that they pose a cardiovascular hazard of similar magnitude to that resulting from being a smoker or having diabetes. [40] In 2015, the U.S. Food and Drug Administration (FDA) strengthened it's warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke.[41] NSAIDs are a common cause of peptic ulcer disease as well as lower tract inflammation.(42) Cumulative NSAID exposure is associated with an increased risk for rapid CKD progression.[43] Despite these known risks, concomitant NSAID use by patients with these chronic conditions is common.[44-46] This risk is particularly high in the elderly.[43] For patients with osteoarthritis, consider physical therapy, tai chi, bracing, steroid injections, acetaminophen, duloxetine or tramadol.[47] Topical diclofenac is an option for patients who require anti-inflammatory therapy for superficial joints like the knee, elbow, wrist and hands.[47,48]

Albuterol

Beta-agonists have long been staple in the management of acute asthma, necessitating every asthma patient to have a rescue albuterol inhaler handy in addition to their maintenance medication. Recent guidelines have de-emphasized the use of lone immediate-release beta-agonists for acute asthma symptoms in favor of a combination inhaled corticosteroids (ICS) and beta-agonists.[49, 50] Formoterol, a long-acting beta-agonist, has been formulated with budesonide as a controller therapy. Formoterol has been shown to have a short onset of action making it appropriate for use in acute asthma. Using Formoterol combination therapy is now recommended for management of acute asthma symptoms rather than a lone short-acting beta agonist. In patients requiring both an ICS + a LABA, formoterol/budesonide can be used for both maintenance and acute symptoms negating the need for an additional albuterol inhaler. For mild to moderate persistent asthma, single maintenance and reliever therapy (SMART) is preferred. As of today, budesonide/formoterol is not approved by the U.S. Food and Drug Administration for use as a quick relief agent.

Stool Softeners

Stool softeners like docusate have been espoused to increase water in stool resulting in a softer stool that is easier to pass. However, there is no strong evidence to support this mechanism of action, and a review of studies from 1956-2021 showed no significant effect in placebo controlled studies.[51] Increasing dietary fiber and water intake are good ways to soften stools.

Sample Closets

Sample drug closets are common in primary care as well as specialty clinics,[52] and while there are theoretical advantages to having sample medications to dispense during an office visit,[53] studies suggest the utility may not outweigh the drawbacks. The dispensing of sample medications has been associated with increased total and out of pocket medication costs, contrary to the perceived intent.[54] Sample closets are associated with lower use of generic medications and lower compliance with treatment guidelines.[55,56] A systematic review of 19 studies of interactions between practicing physicians and pharmaceutical companies found that lower physician prescribing quality was associated with higher industry interactions, including the acceptance of free drug samples.[57]

Summary

Comprehensive medication management includes not only ensuring patients are prescribed the most appropriate medication(s) and dosage for their healthcare needs, but also ongoing monitoring and review to determine when a medication is no longer needed. When the risks of a medication outweigh the benefits or when a medication is responsible for a side effect, deprescribing should be considered.

References

1. Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? Can J Hosp Pharm. 2013 May;66(3):201-2. doi: 10.4212/cjhp.v66i3.1261. PMID: 23814291; PMCID: PMC3694945.
2. Tichy, Eric M, Hoffman, James M, Suda, Katie J, Rim, Matthew H, Tadrous, Mina, Cuellar, Sandra, Clark, John S, Ward, Jennifer, Schumock, Glen T. National trends in prescription drug expenditures and projections for 2022. Am J Health Syst Pharm. 2022.
3. Halli-Tierney A, Scarbrough C, Carroll D. Polypharmacy: Evaluating Risks and Deprescribing. Am Fam Phys 2019:100(1), 32-38.Gnjidic D, Le Couteur D, Pearson S, et al. High risk prescribing in older adults: prevalence, clinical and economic implications and potential for intervention at the population level. BMC Public Health. 2013:13;115.
4. Clark C, Shaver A, Aurelio A, Feuerstein L, et al. Potentially Inappropriate Medications Are Associated with Increased Healthcare Utilization and Costs. J Am Geriatr Soc 2020 Nov;68(11):2542-2550. DOI 10.1111/jgs.16743
5. Leipzig R, Cumming R, Tinetti M. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. . J Am Geriatr Soc 1999:47:40-50.
6. Rochon P. Gurwitz J. Drug Therapy. Lancet 1995;346(8966):32.
7. Vordenberg S, Singer D, Kirch M, Solway E, Roberts S, Smith E, Hutchens L, Malani P, Kullgren J. Views on Medication Deprescribing Among Adults Age 50–80. University of Michigan National Poll on Healthy Aging. April 2023. Available at: https://dx.doi.org/10.7302/7128
8. Vassiliki P. Thoughtful Prescribing and Deprescribing. Med Clin N Am (2020) 751-765.
9. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf. 2017 Sep;8(9):273-297. doi: 10.1177/2042098617715381. Epub 2017 June 29. PMID: 28861211; PMCID: PMC5557164.
10. Hu W, Tong J, Kuang X, Chen W, Liu Z. Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis. Medicine (Baltimore). 2018;97(3):e9638.
11. Targownik L, Fisher D, Saini S. AGA clinical practice update on de-prescribing of proton pump inhibitors: Expert review. Gastroenterology 2022;162:1334-1342.
12. Krebs EE, Gravely A, Nugent S,Jensen AC, DeRonne B, Goldsmith ESet al. Effect of opioid vs non-opioid medications on pain-related function inpatients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. JAMA2018;319: 872–82.
13. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011 Mar-Apr;14(2):145-61. PMID: 21412369.
14. Aili V Langford, Christine CW Lin, Lisa Bero, Fiona M Blyth, Jason Doctor, Simon Holliday, Yun-Hee Jeon, Joanna Moullin, Bridin Murnion, Suzanne Nielsen, Rawa Osman, Jonathan Penm, Emily Reeve, Sharon Reid, Janet Wale, Carl R Schneider and Danijela Gnjidic. Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations. Med J Aust || doi: 10.5694/mja2.52002 Published online: 26 June 2023. Med J Aust || doi: 10.5694/mja2.52002
15. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA 2016;315:1624–45.
16. Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. J Subst Abuse Treat 2019;103:58–63.19 Oliva EM, Bowe T, Manhapra Aet al.Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans:observational evaluation. BMJ 2020;368: m283.
17. Dowell D, Compton WM, Giroir BP.Patient-centered reduction or discontinuation of long-term opioid analgesics: the HHS guide for clinicians.JAMA 2019;322: 1855–6.
18. Frank JW, Lovejoy TI, Becker WC,Morasco BJ, Koenig CJ, Hoffecker Let al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. Ann Intern Med 2017;167: 181–91.

19. McAnally H, Bonnet U, Kaye AD. Gabapentinoid Benefit and Risk Stratification: Mechanisms Over Myth. Pain Ther. 2020 Dec;9(2):441-452. doi: 10.1007/s40122-020-00189-x. Epub 2020 Jul 31. Erratum in: Pain Ther. 2021 Jun;10(1):763-764. PMID: 32737803; PMCID: PMC7648827.

20. Chen C, Winterstein AG, Lo-Ciganic WH, Tighe PJ, Wei YJ. Concurrent use of prescription gabapentinoids with opioids and risk for fall-related injury among older US Medicare beneficiaries with chronic noncancer pain: A population-based cohort study. PLoS Med. 2022 Mar 1;19(3):e1003921. doi: 10.1371/journal.pmed.1003921. PMID: 35231025; PMCID: PMC8887769.

21. Anderson PA, McLachlan AJ, Abdel Shaheed C, Gnjidic D, Ivers R, Mathieson S. Deprescribing interventions for gabapentinoids in adults: A scoping review. Br J Clin Pharmacol. 2023 Sep;89(9):2677-2690. doi: 10.1111/bcp.15798. Epub 2023 Jun 13. PMID: 37221314.

22. Kasper S, Iglesias-Garcia C, Schweizer E, et al. Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. Int J Neuropsychopharmacol. 2014; 17(5): 685-695. doi:10.1017/S1461145713001557

23. FDA Drug Safety Communication: Ongoing safety review of oral osteoporosis drugs (bisphosphonates) and potential increased risk of esophageal cancer. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-safety-update-osteoporosis-drugs-bisphosphonates-and-atypical

24. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2016;31:16–35. http://dx.doi.org/10.1002/jbmr.2708

25. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, Feldstein A, Haskell WL, Hochberg MC, Torner JC, Lombardi A, Black DM; Fracture Intervention Trial Long-Term Extension Research Group. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res. 2004 Aug;19(8):1259-69. doi: 10.1359/JBMR.040326. Epub 2004 Mar 29. PMID: 15231012.

26. Adler R, Fuleihan G, Bauer D, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research, Vol. 31, No. 1, January 2016, pp 16–35. https://doi.org/10.1002/jbmr.2708

27. Eriksen EF, Díez-Pérez A, Boonen S. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review. Bone 2014;58:126–35. http://dx.doi.org/10.1016/j.bone.2013.09.023

28. US Preventive Services Task Force. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. JAMA. 2022;327(16):1577–1584. doi:10.1001/jama.2022.4983

29. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

30. Schaefer JK, Errickson J, Gu X, et al. Assessment of an Intervention to Reduce Aspirin Prescribing for Patients Receiving Warfarin for Anticoagulation. JAMA Netw Open. 2022;5(9):e2231973. doi:10.1001/jamanetworkopen.2022.31973

31. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2016;165(2):125. Epub 2016 May 3.

32. De Crescenzo F, D'AlòGL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, Kurtulmus A, Tomlinson A, Mitrova Z, Foti F, Del Giovane C, Quested DJ, Cowen PJ, Barbui C, Amato L, Efthimiou O, Cipriani A. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022;400(10347):170

33. Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA, Welch V, Holbrook A, Boyd C, Swenson R, Ma A, Farrell B. Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. Can Fam Physician. 2018 May;64(5):339-351. PMID: 29760253; PMCID: PMC5951648.

34. Gelenberg A, Freeman M, Markowitz J, Rosenbaum J, et al. APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd Edition. October 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ mdd-1410197717630.pdf

35. Buckman JEJ, Underwood A, Clarke K, Saunders R, Hollon SD, Fearon P, Pilling S. Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. Clin Psychol Rev. 2018 Aug;64:13-38. doi: 10.1016/j.cpr.2018.07.005. Epub 2018 Jul 29. PMID: 30075313; PMCID: PMC6237833.

36. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19(Suppl.): 789–830.

37. van Dalem J, Brouwers MC, Stehouwer CD, Krings A, Leufkens HG, Driessen JH, de Vries F, Burden AM. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. BMJ. 2016 Jul 13;354:i3625. doi: 10.1136/bmj.i3625. PMID: 27413017; PMCID: PMC4948031.

38. A. S. Abdelmoneim, D.T. Eurich, P.E. Light ,P.A.Senior, J.M. Seubert, M.J. Makowsky, S. H. Simpson. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes, Obesity and Metabolism 17: 523–532, 2015.

39. Genuth S. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? No, it's time to move on! Diabetes Care. 2015 Jan;38(1):170-5. doi: 10.2337/dc14-0565. PMID: 25538314.

40. Liantonio J, Simmons B. NSAIDs and the Geriatric Patient: A Cautionary Tale. Consultant 360 Vol. 21 No. 5 May 2013. Available at: https://www.consultant360.com/articles/nsaids-and-geriatric-patient-cautionary-tale Accessed 9/25/23.

41. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory

42. Tai F, McAlindon M. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clinical Medicine 2021 Vol 21, No 2: 131–4. DOI: 10.7861/clinmed.2021-0039

43. Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, Frank C, Klarenbach S, Hemmelgarn BR. NSAID use and progression of chronic kidney disease. Am J Med. 2007 Mar;120(3):280.e1-7. doi: 10.1016/j.amjmed.2006.02.015. PMID: 17349452.

44. Lefebvre C, Hindié J, Zappitelli M, Platt RW, Filion KB: Non-steroidal anti-inflammatory drugs in chronic kidney disease: A systematic review of prescription practices and use in primary care. Clin Kidney J 13: 63–71, 2019.

45. Adams RJ, Appleton SL, Gill TK et al. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community—a population-based study. BMC Family Practice 2011, 12:70 http://www.biomedcentral.com/1471-2296/12/70

46. Guthrie B. Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: CON. Kidney360. 2020 Sep 23;1(11): 1189-1191. doi: 10.34067/KID.0005112020. PMID: 35372868; PMCID: PMC8815518

47. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 Feb;72(2):149-162. doi: 10.1002/acr.24131. Epub 2020 Jan 6. Erratum in: Arthritis Care Res (Hoboken). 2021 May;73(5):764. PMID: 31908149.

48. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2012 Sep 12;9(9):CD007400. doi: 10.1002/14651858.CD007400.pub2. Update in: Cochrane Database Syst Rev. 2016;4:CD007400. PMID: 22972108; PMCID: PMC4160008.

49. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. 2022. Available from www.ginasthma.org

50. Cloutier MM, Baptist AP, Blake KV, et al; Expert Panel Working Group of the National Heart, Lung, and Blood Institute administered and coordinated National Asthma Education and Prevention Program Coordinating Committee; 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group [published correction appears in J Allergy Clin Immunol. 2021;147(4):1528–1530]. J Allergy Clin Immunol. 2020;146(6):1217-1270.

51. McRorie JW, Petrey ME, Sloan KJ, Gibb RD. Docusate is not different from placebo for stool softening: a comprehensive review. American journal of gastroenterology, 2021, 116(SUPPL), S85.

52. Campbell EG, Rao SR, DesRoches CM, et al. Physician professionalism and changes in physician-industry relationships from 2004–2009. Arch Int Med 2010;170:1820–6.

53. Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. J Gen Intern Med 2000;15:478–83.

54. Evans KL, Brown SR, Smetana GW. Sample closet medications are neither novel nor useful. J Am Board Fam Med. 2013 Jul-Aug;26(4):380-7. doi: 10.3122/jabfm.2013.04.120330. PMID: 23833152.

55. Miller DP, Mansfield RJ, Woods JB, Wofford JL, Moran WP. The impact of drug samples on prescribing to the uninsured. South Med J. 2008 Sep;101(9):888-93. doi: 10.1097/SMJ.0b013e3181814d52. PMID: 18708971.

56. Pinckney RG, Helminski AS, Kennedy AG, Maclean CD, Hurowitz L, Cote E. The effect of medication samples on self-reported prescribing practices: a statewide, cross-sectional survey. J Gen Intern Med. 2011 Jan;26(1):40-4. doi: 10.1007/s11606-010-1483-x. Epub 2010 Aug 31. PMID: 20809157; PMCID: PMC3024102.

57. Brax H, Fadlallah R, Al-Khaled L, Kahale LA, Nas H, El-Jardali F, Akl EA. Association between physicians' interaction with pharmaceutical companies and their clinical practices: A systematic review and meta-analysis. PLoS One. 2017 Apr 13;12(4):e0175493. doi: 10.1371/journal.pone.0175493. PMID: 28406971; PMCID: PMC5391068.