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Clinical Decision Support Tools for Prescribing High-Alert Medications

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Disclosure & Disclaimer Statement

"We do not have any relevant financial relationships with any commercial interests."

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3 Educational Objectives

- Learning Objective 1: **Review the Institute for Safe Medication Practices high-alert medication classes and specific high-alert medications**

- Learning Objective 2: **Describe the potential effects of clinical inertia and deprescribing**

- Learning Objective 3: **Explore ways to apply clinical decision support tools and disease registries in correctional health care**

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ISMP Background

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Background

Based on error reports submitted to the ISMP National Medication Errors Reporting Program (ISMP MERP), reports of harmful errors in the literature, studies that identify the drugs most often involved in harmful errors, and input from practitioners and safety experts, ISMP created and periodically updates a list of potential high-alert medications. During June and July 2018, practitioners responded to an ISMP survey designed to identify which medications were most frequently considered high-alert medications. Further, to assure relevance and completeness, the clinical staff at ISMP and members of the ISMP advisory board were asked to review the potential list. This list of medications and medication categories reflects the collective thinking of all who provided input.

Practitioners: Physicians, Pharmacist and
Patient Safety Experts
Literature
Error reports
Collective thinking

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Institute for Safe Medication Practices
An ECRI Affiliate

Clinical Decision Support Tools

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ISMP List of High-Alert Medications
in Community/Ambulatory Care Settings

High-Alert Medications
in Long-Term Care (LTC) Settings

ISMP List of High-Alert Medications
in Acute Care Settings

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ISMP Introductory Paragraph for all 3 Venues

- High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error.
- Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients.
- We hope you will use this list to determine which medications require special safeguards to reduce the risk of errors.
- This may include strategies such as standardizing the prescribing, storage, preparation, and administration of these products; improving access to information about these drugs; limiting access to certain high-alert medications; using auxiliary labels; employing clinical decision support and automated alerts; and using redundancies such as automated or independent double checks when necessary.
- (Note: manual independent double checks are not always the optimal error-reduction strategy and may not be practical for all of the medications on the list.)

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Community/ Ambulatory Care

Antithrombotic agents, oral and parenteral, including:

- Anticoagulants (e.g., warfarin, low molecular weight heparin, unfractionated heparin)
- Direct oral anticoagulants and factor Xa inhibitors (e.g., dabigatran, rivaroxaban, apixaban, edoxaban)
- Direct thrombin inhibitors (e.g., dabigatran)

Chemotherapeutic agents

- Oral and parenteral chemotherapy (e.g., capecitabine, cyclophosphamide)
- Oral targeted therapy and immunotherapy (e.g., palbociclib [**IBRANCE**], imatinib [**GLEEVEC**], bosutinib [**BOSULIF**])
- Excludes hormonal therapy

Immunosuppressant agents, oral and parenteral (e.g., aza**THIO**prine, cyclo**SPORINE**, tacrolimus)

Insulins, all formulations and strengths (e.g., U-100, U-200, U-300, U-500)

Medications contraindicated during pregnancy (e.g., bosentan, **ISO**tretinoin)

Moderate and minimal sedation agents, oral, for children (e.g., chloral hydrate, midazolam, ketamine [using the parenteral form])

Opioids, all routes of administration (e.g., oral, sublingual, parenteral, transdermal), including liquid concentrates, immediate- and sustained-release formulations, and combination products with another drug

Pediatric liquid medications that require measurement

Sulfonylurea hypoglycemics, oral (e.g., chlorpro**PAMIDE**, glimepiride, gly**BURIDE**, glipi**ZIDE**, **TOLBUT**amide)

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Long Term Care (LTC)

Classes/Categories of Medications
• Anti-Parkinson's drugs, including carbidopa, levodopa, and combination products that contain at least one of these ingredients
• Antithrombotic agents, parenteral and oral, including: ▪ anticoagulants (e.g., warfarin, low molecular weight heparin, unfractionated heparin) ▪ direct oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban) ▪ direct thrombin inhibitors (e.g., dabigatran)
• Chemotherapeutic agents ▪ Oral and parenteral chemotherapy (e.g., capecitabine, cyclophosphamide) ▪ Oral targeted therapy and immunotherapy (e.g., palbociclib [**IBRANCE**], imatinib [**GLEEVEC**], bosutinib [**BOSULIF**]) ▪ Excludes hormonal therapy
• GABA analogs (e.g., gabapentin, pregabalin) used to treat neuropathic pain
• Immunosuppressants, oral and parenteral (e.g., aza**THIO**prine, cyclo**SPORINE**, cyclophosphamide, tacrolimus, abatacept [**ORENCIA**], adalimumab [**HUMIRA**])
• Insulins, all formulations and strengths (e.g., U-100, U-200, U-300, U-500)
• Opioids, all routes of administration (e.g., oral, sublingual, parenteral, transdermal), including liquid concentrates, immediate- and sustained-release formulations, and combination products with another drug
• Parenteral nutrition preparations
• Sulfonylurea hypoglycemics, oral (e.g., chlorpro**PAMIDE**, glimepiride, gly**BURIDE**, glipi**ZIDE**, **TOLBUT**amide)

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Acute Care

Classes/Categories of Medications
adrenergic agonists, IV (e.g., **EPINEPH**rine, phenylephrine, norepinephrine)
adrenergic antagonists, IV (e.g., propranolol, metoprolol, labetalol)
anesthetic agents, general, inhaled and IV (e.g., propofol, ketamine)
antiarrhythmics, IV (e.g., lidocaine, amiodarone)
antithrombotic agents, including: ■ anticoagulants (e.g., warfarin, low molecular weight heparin, unfractionated heparin) ■ direct oral anticoagulants and factor Xa inhibitors (e.g., dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban, fondaparinux) ■ direct thrombin inhibitors (e.g., argatroban, bivalirudin, dabigatran) ■ glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide) ■ thrombolytics (e.g., alteplase, reteplase, tenecteplase)
cardioplegic solutions
chemotherapeutic agents, parenteral and oral
dextrose, hypertonic, 20% or greater
dialysis solutions, peritoneal and hemodialysis
epidural and intrathecal medications
inotropic medications, IV (e.g., digoxin, milrinone)
insulin, subcutaneous and IV
liposomal forms of drugs (e.g., liposomal amphotericin B) and conventional counterparts (e.g., amphotericin B desoxycholate)
moderate sedation agents, IV (e.g., dexmedetomidine, midazolam, **LOR**azepam)
moderate and minimal sedation agents, oral, for children (e.g., chloral hydrate, midazolam, ketamine [using the parenteral form])
opioids, including: ■ IV ■ oral (including liquid concentrates, immediate- and sustained-release formulations) ■ transdermal
neuromuscular blocking agents (e.g., succinylcholine, rocuronium, vecuronium)
parenteral nutrition preparations
sodium chloride for injection, hypertonic, greater than 0.9% concentration
sterile water for injection, inhalation and irrigation (excluding pour bottles) in containers of 100 mL or more
sulfonylurea hypoglycemics, oral (e.g., chlorpro**PAMIDE**, glimepiride, gly**BURIDE**, glipi**ZIDE**, **TOLBUT**amide)

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Common Classes

Medication classes on all three lists

i. Antithrombotic

ii.Chemotherapeutic

iii.Sulfonylureas

iv.Insulins

v.Opioids

*Drugs contraindicated in pregnancy and Immunosuppressant were on the two outpatient settings

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ISMP High Alert Specific Medications ACS

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Specific Medications

CarBAMazepine

EPINEPHrine, IM, subcutaneous

Insulin U-500 (special emphasis)*

LamoTRIgine

Methotrexate, oral and parenteral, nononcologic use (special emphasis)*

Phenytoin

Valproic acid

Specific Medications

- Concentrated morphine solution (20 mg/mL), oral (special emphasis)*
- Digoxin, parenteral and oral
- EPINEPHrine, IM, subcutaneous
- Insulin U-500
- Iron dextran, parenteral
- Methotrexate, oral and parenteral, nononcologic use (special emphasis)*
- Phenytoin
- Sacubitril and valsartan (ENTRESTO)

Specific Medications

EPINEPHrine, IM, subcutaneous

epoprostenol (e.g., Flolan), IV

insulin U-500 (special emphasis*)

magnesium sulfate injection

methotrexate, oral, nononcologic use

nitroprusside sodium for injection

opium tincture

oxytocin, IV

potassium chloride for injection concentrate

potassium phosphates injection

promethazine injection

vasopressin, IV and intraosseous

Common Specific Medications

Common Specific medications

i. Epinephrine

ii. Insulin U-500

iii. Methotrexate for non-oncology use

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ISMP “Other Resources for LTC Facilities”

- Facilities are also encouraged to use other resources, such as the Beers Criteria1,2 and STOPP and START Criteria 3 to identify and address medications that should be avoided in the elderly population, which are different than high-alert medications.

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STOPP/START Criteria

- STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people
- Pages 15-22 | Received 12 Sep 2019, Accepted 22 Nov 2019, Published online: 30 Nov 2019
- In single-center trials, applying STOPP/START criteria improved medication appropriateness, reduced polypharmacy, reduced adverse drug reactions (ADRs), led to fewer falls, and lower medication costs.
- Two large-scale multi-center trials (SENATOR and OPERAM) examined the impact of computer-generated STOPP/START criteria on incident ADRs (SENATOR) and drug-related hospitalizations (OPERAM) in multi-morbid older people.

SENATOR Trial

- Multi-morbidity and polypharmacy increase the risk of non-trivial adverse drug reactions (ADRs) in older people during hospitalization.
- **Methods:** We undertook a pragmatic, multi-national, parallel arm prospective randomized open-label, blinded endpoint (PROBE) controlled trial enrolling patients at six European medical centres.
- We randomized 1,537 older medical and surgical patients with multi-morbidity and polypharmacy on admission in a 1:1 ratio to SENATOR software-guided medication optimization plus standard care (intervention, n = 772, mean number of daily medications = 9.34) or standard care alone (control, n = 765, mean number of daily medications = 9.23)

SENATOR Trial

- **Results:** For the primary endpoint, there was no difference between the intervention and control groups (24.5 vs. 24.8%; OR 0.98; 95% CI 0.77-1.24; P = 0.88). Similarly, with secondary and tertiary endpoints, there were no significant differences. Among attending clinicians in the intervention group, implementation of SENATOR software-generated medication advice points was poor (~15%).
- **Conclusions:** In this trial, uptake of software-generated medication advice to minimize ADRs was poor and did not reduce ADR incidence during index hospitalization.
- Alert Fatigue

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OPERAM

- Medication review was performed jointly by a physician and pharmacist **(i.e. pharmacotherapy team)** supported by a Clinical Decision Support System with integrated STOPP/START criteria.
- Individualized STOPP/START-based medication optimization recommendations were discussed with patients and attending hospital physicians.

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OPERAM Results

- 139 patients were included, mean (SD) age 78.3 (5.1) years, 47% male and median (IQR) number of medications at admission 11 (9–14).
- In total, 371 recommendations were discussed with patients and physicians, overall agreement was 61.6% for STOPP and 60.7% for START recommendations.
- Highest agreement was found for initiation of osteoporosis agents and discontinuation of proton pump inhibitors (both 74%).
- Factors associated with higher agreement in multivariate analysis were: female gender (+ 17.1% [3.7; 30.4]), ≥ 1 falls in the past year (+ 15.0% [1.5; 28.5]) and renal impairment i.e. eGFR 30–50 ml/min/1.73 m²; (+ 18.0% [2.0; 34.0]).
- The main reason for disagreement (40%) was patients' reluctance to discontinue or initiate medication.

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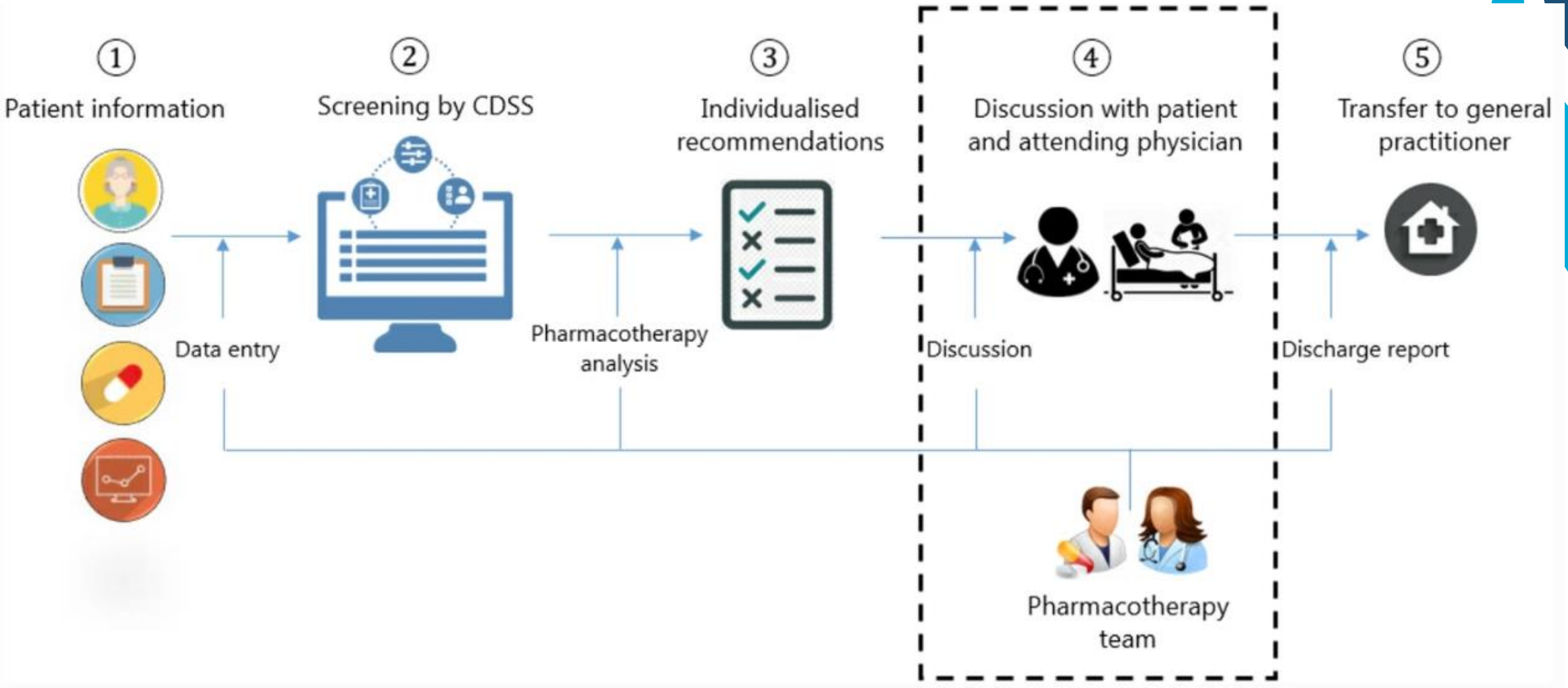

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2019 AGS Beers Criteria®

A Guide for Patients, Clinicians, Health Systems, and Payors

Purposes:

1. Identifies potentially inappropriate medications that should be avoided
2. Reduces adverse drug events & drug related problems - improves medication selection and medication use
3. An educational, quality, and research tool, designed for use in any clinical setting

American Geriatric Society
Aging of Incarcerated Population

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Key Principles

The AGS Beers Criteria® (CDS) are intended to support, not contradict, common sense and good clinical care

1. Medications in the 2019 AGS Beers Criteria® are *potentially* inappropriate, not *definitely* inappropriate.
2. Read the rationale and recommendations statements for each criterion. The caveats and guidance listed there are important.
3. Understand why medications are included in the 2019 AGS Beers Criteria®, and adjust your approach to those medications accordingly.
4. Optimal application of the 2019 AGS Beers Criteria® involves … offering safer non-pharmacologic and pharmacologic therapies.
5. The 2019 AGS Beers Criteria® should be a starting point for a comprehensive process of identifying and improving medication appropriateness and safety.
6. Access to medications included in the 2019 AGS Beers Criteria® should not be excessively restricted by prior authorization and/or health plan coverage policies.
7. The 2019 AGS Beers Criteria® are not equally applicable to all countries. (Global)

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Medication Reconciliation to Prevent Adverse Drug Events

- Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking — including drug name, dosage, frequency, and route
- The goal of providing correct medications to the patient at all transition points within the facility.
- Admission, transfer, and/or discharge orders

https://www.ihi.org/

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The medication reconciliation process involves three steps:

1. Verification (collection of the medication history)

2. Clarification (ensuring that the medications and doses are appropriate)

3. Reconciliation (documentation of changes in the orders)

How-to Guide: Prevent Adverse Drug Events by Implementing Medication Reconciliation. Cambridge, MA: Institute for Healthcare Improvement; 2011. (Available at www.ihi.org)

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Medication Reconciliation should occur at each fresh point of contact with a patient:

1. Admission: Inventory and documentation of home medications, then reconcile with other medication records on file and new medication orders.

1. Transfer: Review previous medication orders in light of new orders or plans of care, resolve any conflicts, changes or omissions and document the resolution.

2. Discharge: Review and update all medications the patient was taking at home, incorporating new prescriptions to ensure that all medications are clearly noted for continuation or discontinuation and that recommended changes are explained.

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Clinical Inertia and Deprescribing

- **Medical culture and clinical inertia** — Medical culture has been highlighted as a barrier to deprescribing, including a historically clinician-centric culture where prescribing is a central part of professional identity.
- Additionally, starting a medication is familiar and considered a positive action (ie, doing something to help the patient), while deprescribing is less familiar and may be considered a lower priority or as withdrawing care.
- Clinical inertia (continuation along a path of treatment without re-evaluation or staying with the “status quo”) is also common in medical culture and can discourage deprescribing.

UpToDate: Accessed 10.10.22 Literature review current through: **Sep 2022.**
This topic last updated: **Apr 22, 2021.**

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Clinical Inertia and Deprescribing

- Strategies to combat clinical inertia and cultural norms and increase the normality of deprescribing include:
  - Equally considering the benefits and harms of continuation against the benefits and harms of discontinuation.
  - Attending deprescribing-related continuing education opportunities and advocating for greater undergraduate teaching of deprescribing.
  - Discussing deprescribing activities with colleagues, including success stories.

Deprescribing

- Deprescribing is an essential part of good prescribing and is inherently linked to related activities, such as medication reconciliation, to ensure safe and effective use of medications.
- This process requires attention, time, and in many cases special skills and knowledge.
- This includes technical knowledge, such as optimal down-titration schedules, as well as competencies in shared decision-making, communication, and managing health systems in a medical culture that historically has been more oriented toward adding medications than stopping them

Patient with Rheumatoid Arthritis

- 50+ year old Caucasian male
- Ferrous Sulfate 325 QD
- Indocin 50 mg tid
- Omeprazole 40 mg QD
- (Adalimumab) Humira 40mg/0.8 ml; give 0.8 ml twice monthly

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Clinical Decision Support Tools

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The main purpose of CDS is to provide timely information to clinicians, patients, and others to inform decisions about health care. Examples of CDS tools include order sets created for particular conditions or types of patients, recommendations, and databases that can provide information relevant to particular patients, reminders for preventive care, and alerts about potentially dangerous situations.

Agency for Healthcare Research and Quality

Disease Registry

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“A **disease registry** is a tool for tracking the clinical care and outcomes of a defined **patient population**. Most **disease registries** are used to support care **management** for groups of patients with one or more chronic **diseases**, such as diabetes, coronary artery **disease**, or asthma.”

Agency for Healthcare Research and Quality (AHRQ)

ISMP High Alert Specific Medications
Methotrexate for Non-oncology use

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Dosing: Adult (Methotrexate)
Note: Safety: Fatal errors have occurred when methotrexate was administered as a **daily** dose instead of a **weekly** dose. Verify the indication before administration; oral methotrexate is typically only administered **daily** for an oncology-related indication (ISMP 2020). Patient should be under the care of a clinician experienced with using methotrexate.

15 oncology indication and 20 non-oncology indications

Methotrexate Non-Oncology FDA Approved

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Psoriasis, moderate to severe:
Note: Patient should be under the care of a clinician experienced with using methotrexate for this condition.
Oral, IM, SUBQ: Initial: 10 to 15 mg once **weekly**. Adjust dose gradually (eg, every 4 to 8 weeks) if needed based on response (usual dosage range: 7.5 to 25 mg/**week**) (AAD/NPF [Menter 2020]; Feldman 2021).
Rheumatoid arthritis:
Note: Patient should be under the care of a clinician experienced with using methotrexate for this condition.
Oral, SUBQ, IM: Initial: 7.5 to 15 mg once **weekly**. Increase dose by 2.5 to 5 mg/**week** every 4 to 12 weeks if needed based on response (maximum: 25 mg/**week**); current guidelines suggest titrating to a target dose of ≥15 mg/**week** within 4 to 6 weeks of initiation. Once disease remission is achieved, may gradually reduce dose (eg, by 2.5 mg/**week** every 1 to 2 months) to 15 mg/**week** to limit adverse effects (ACR [Fraenkel 2021]; Braun 2008; Cohen 2021; EULAR [Smolen 2017]; Kremer 2021).

Methotrexate Non-Oncology Use

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Nononcologic uses:
Note: During **chronic** therapy, treat with folic acid to reduce the risk of adverse effects; leucovorin may be considered in patients who do not respond to folic acid

Renal
Aronoff 2007:
CrCl >50 mL/minute: No dose adjustment necessary.
CrCl 10 to 50 mL/minute: Administer 50% of dose.
CrCl <10 mL/minute: Avoid use.
Hemodialysis, intermittent (thrice weekly):
Cases of methotrexate toxicity (including death) have been reported in hemodialysis patients receiving methotrexate, even at low methotrexate doses. Avoid use (Al-Hasani 2011; Basile 2002).

Methotrexate Non-Oncology Use

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Dosing: Hepatic Impairment:

Adult

Hepatic impairment prior to treatment: There are no dosage adjustments provided in the manufacturer's labeling; use with caution and consider a reduced dose in patients with impaired hepatic function or preexisting hepatic damage. The following adjustments have been recommended (Floyd 2006):

Bilirubin 3.1 to 5 mg/dL **or** transaminases >3 times ULN: Administer 75% of dose.

Bilirubin >5 mg/dL: Avoid use.

Hepatotoxicity during treatment: Withhold, consider a reduced dose, or discontinue methotrexate as appropriate.

Methotrexate Non-Oncology Use

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Registry Data

- Currently 18 patients with following dx:
  - (6) Psoriasis
  - (1) Psoriatic Arthritis
  - (6) RA
  - (3) Sarcoidosis
  - (2) Crohn's

- 16/18 patients receiving folic acid
- 16/18 dosed every week
  - Three times a week
- 1/18 with GFR<60
- 2/18 with AST >40

ACCP Position Statement on HCV Disease

- American College of Correctional Physician "believes that prison systems should establish a multidisciplinary HCV committee to incorporate the evidence-based standard of care into treatment plans for patients, similar to hospital tumor boards.
- Structure Process Outcome
- Data evaluating tumor boards — particularly, the extent to which these conversations among specialists improve patient outcomes — remain mixed.

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Multidisciplinary

- One study, published in *BMJ*, found that after introducing multidisciplinary oncology care in hospitals in Scotland, breast cancer mortality was 18% lower among patients who received the team-based intervention.
- A 2019 analysis, for instance, indicated that the 5-year survival rate was 15.6% higher among cases in well-organized multidisciplinary tumor groups but almost 20% lower in disorganized groups compared with no tumor board.

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Conclusion: Execution Curiosity and Humility

- "Execution of the plan is how we get to good outcomes regardless of the brilliance of the plan, the talent of the team, or the difficulty of the task.“
- “A spirit of curiosity" is critical to a high-functioning tumor board, said Kamal. "It's important to remember that you're there to learn from colleagues."
- Plus, "a dose of humility can help," McClelland said.

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