First Do No Harm
Psychotropic Prescribing Principles and Guidelines for Older Adults

ABSTRACT

The drive to prescribe to alleviate symptoms and ease suffering is prevalent in health care. In psychiatry, it is no different. Although monotherapy remains the preferred approach to treating psychiatric disorders, especially when combined with nonpharmacological approaches, in practice, a focus on remission of symptoms over patient preferences and quality of life can result in higher doses than necessary and polypharmacy from the addition of drugs for augmentation or treatment of adverse effects. This is especially concerning for older adults who are likely to have comorbid medical disorders, eventually leading to prescribing cascades as different providers address different symptoms. Whereas we generally look to best practice guidelines to treat identified disorders, the approach to treating older adults with multimorbidities requires collaboration among the patient, the family (if appropriate), and the provider to re-evaluate goals based on the patient's priorities, and to examine tradeoffs, reduce medication overload, and simplify care. Fortunately, many resources are available to help the clinician in this process. [*Journal of Psychosocial Nursing and Mental Health Services, 58*(8), 12–16.]

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Older adults are more likely than younger adults to have multiple chronic conditions, multiple health care providers, and complex drug regimens with polypharmacy. In the United States, >40% of older adults take five or more medications daily, and >20% take 10 or more (Lown Institute, 2019). Psychotropic medications are especially concerning. In a recent survey of U.S. older homebound adults with depressive symptoms, >50% were taking antidepressants, >40% opioids, >20% were using sedative hypnotics, and approximately 16% were taking three or more psychotropic medications (Choi et al., 2020). Older adults who report anxiety or distress are frequently treated with psychotropic drugs, despite lack of evidence for a diagnosable disorder (Bobo et al., 2019). In addition to scheduled medications, older adults in long-term care, and possibly at home, may be taking multiple pro re nata (PRN) medications (Dörks et al., 2019) to treat acute symptoms of anxiety, insomnia, and aggressive behavior.

Chronic medical conditions, such as cardiovascular disease and diabetes, are associated with depressive symptoms and reduced quality of life in older adults (Gallo, 2017). Older adults may also have chronic mental disorders that pre-date older adulthood or begin in older adulthood. The prevalence of diagnosable mental disorders among older adults in the U.S. National Survey on Drug Use and Mental Health

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(Substance Abuse and Mental Health Services Administration, 2018) was 2.7%, and the prevalence with serious mental illness was 13.8%. The majority of those with serious mental illness and approximately 44% of those with other diagnosable mental disorders were treated for their conditions, presumably with psychotropics.

Jacobson (2013) describes pharmacokinetic changes of normal aging that increase the risk for adverse drug effects. *Absorption*, the time it takes for a drug to take effect, may be affected by diseases or drugs that affect gastric motility and emptying. Once absorbed from the gastrointestinal tract into the portal circulation, most psychotropics will enter first-pass metabolism, commonly by the cytochrome P450 (CYP450) enzymes, in the liver. Six CYP450 enzymes are clinically relevant in the first-pass metabolism of psychotropic drugs: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Of these, CYP1A2 and CYP3A decline with aging. The portion of a drug that is metabolized in the liver is excreted directly by the kidneys. Drugs that are not metabolized pass into general circulation and are distributed to organs, storage sites, the kidneys, or the liver. With polypharmacy, the risk of two or more substrate drugs for a specific CYP450 enzyme increase—potentiating the risk for a greater amount of the drug to be passed into general circulation. In addition, with aging, lean body mass decreases and fat stores increase. This is important in psychiatry because most psychotropic drugs are fat-soluble and therefore remain in the body longer in older adults.

Drugs are cleared from the circulation by renal and hepatic metabolism. With aging, the glomerular filtration rate falls linearly to be approximately one half of what it was at age 30 by age 80. Reduced clearance with aging is especially relevant with drugs that are cleared solely by renal excretion (e.g., lithium, nonsteroidal anti-inflammatory drugs). Hepatic clearance

may be reduced by 50% in older adults. With reduced clearance, drug concentrations, half-lives, and time to washout remain elevated for longer periods of time.

For each drug taken by an older adult, the odds of a serious adverse event increase by 7% to 10% (Lown Institute, 2019). Adverse events can be pharmacokinetic or pharmacodynamic. Drugs that decrease the absorption rate (e.g., antacids) of psychotropic drugs may delay the detection of adverse effects. Drugs that inhibit CYP450 enzymes that are required for metabolism of substrate drugs increase the concentration in the general circulation and risk for adverse effects. Drugs that induce CYP450 enzymes that are required for metabolism of substrate drugs decrease the blood concentration and the possibility of therapeutic effects. Psychodynamic drug–drug interactions can occur with additive or inhibitory effects of multiple drugs on target transporters, receptors, and enzymes.

Whereas we generally look to best practice guidelines for treatment advice, older adults with multimorbidity are largely underrepresented in the best practice guidelines that typically focus on a single disorder. The purpose of the current article is to examine the available prescribing principles, guidelines, and resources for rational prescribing for older adults with psychiatric comorbidities. The overall goal of treatment with psychotropics is reduction in symptoms, improved functioning and quality of life, and, at times, reduced mortality rate (Gallo, 2017).

PRESCRIBING PRINCIPLES AND GUIDELINES

In 2019, the American Geriatric Society (AGS) published the updated Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. The criteria are intended as a guide for clinicians working with older adults with goals of improving medication selection and reducing adverse drug effects. The criteria include po-

tentially inappropriate drugs to be used with caution or avoided when treating older adults, older adults with specific disease, and older adults taking other specific medications.

Two frameworks that use the Beers Criteria and other current resources on treatment of older adults with multimorbidities to develop clinician action steps were published by interdisciplinary groups (Boyd et al., 2019; Ouellet et al., 2018) and include a similar three-step process for prescribing.

Step 1. Gather Information (Ouellet et al., 2018) – Identify and Communicate (Boyd et al., 2019). The first step is to gather information about the patient's health priorities for outcome goals, health care preferences, and health trajectory/life expectancy. A Patient Priorities Care approach (Tinetti et al., 2019) is recommended to determine what matters most to the patient, what the patient is willing to do, and the likely health trajectory. In a qualitative analysis of data from interviews with older adults with high-cost multimorbidities, what mattered most to participants fell into eight categories: (a) alleviating discomfort, (b) having autonomy and control, (c) decreasing treatment burden, (d) maintaining physical functioning and engagement, (e) leaving a legacy, (f) extending life, (g) having satisfying and effective relationships, and (h) experiencing security (Wyman et al., 2020). What matters most may not be a longer life, but more short-term improvements in quality of life. How much the older adult is willing to participate in pharmacological or nonpharmacological treatments for mental disorders is likely to involve a weighing of goals, total treatment burden, risks and benefits/key tradeoffs, and quality of life. The outcome of this first collaborative data-gathering step is to develop specific, measurable, actionable, realistic, and time-limited (SMART) goals for treatment.

Step 2. Consider Tradeoffs (Ouellet et al., 2018) – Decide (Boyd et al.,

2019). Before making a decision about whether to stop, start, or continue care, key tradeoffs regarding benefits versus harm and treatment burden must be examined. The five major central nervous system (CNS) active/psychotropic drug categories identified as potentially inappropriate for older adults are anticholinergics, antidepressants, antipsychotics, benzodiazepines, and opioids (AGS Beers Criteria® Update Expert Panel, 2019). Beers Criteria identify drugs that should be avoided regardless of medical conditions, drugs that should be avoided or used with caution in some medical conditions, and drug–drug combinations that should be avoided. Drugs that may exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia include antipsychotics, carbamazepine, mirtazapine, oxcarbazepine, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). Not listed in Beers Criteria is the U.S. Food & Drug Administration (2016) warning for citalopram at doses >20 mg daily for older adults due to the risk for dangerous QTc prolongation.

Most psychotropic drug–drug interactions are a result of metabolic processes (Jacobson, 2013). After reviewing all medications that the patient is taking, the use of a table, such as the drug interactions table (i.e., Flockhart Table™) updated and maintained by the Clinical Pharmacology Division of Indiana University can be helpful in identifying which drugs may be likely to interact. For example, >60 drugs, and many psychotropics, are 2D6 substrates. Bupropion, fluoxetine, and paroxetine are strong inhibitors of 2D6 and may increase the plasma level of the substrate by five-fold or decrease clearance by 80% (Indiana University Clinical Pharmacology Division of the Department of Medicine, 2020). Therefore, for older adults who are likely to be prescribed a 2D6 sub-

strate, these three drugs are not the best choices for treatment. Carbamazepine induces metabolism via 1A2, 2B6, 2C9, and 2C19; thus, when given concurrently with other drugs that use one or more of the enzymes, the dosage of drug may need to be increased. When there is likelihood for CYP450 drug–drug interaction, the table is useful for selecting safer alternatives.

Step 3. Align (Boyd et al., 2019) – Serial Coordinated Therapeutic Trials (Ouellet et al., 2018). Boyd et al. (2019) recommend that decisions regarding care should be aligned among patients, their caregivers, and their providers. Everyone should use the same information regarding what matters most to the patient, the tradeoffs between different approaches and the goals of safe treatment, and quality of life. Guidelines for rational prescribing for older adults with multimorbidity include *deprescribing*, the process of withdrawal or dose reduction of medications that are considered unnecessary or inappropriate. Deprescribing should be considered after careful assessment of the patient's overall health, preferences, medications prescribed, medication adherence, and life trajectory. Many medications can be safely removed (Gupta & Cahill, 2016; Ouellet et al., 2018).

The Screening Tool of Older Person's Potentially Inappropriate Prescriptions and the Screening Tool of Alert Doctors to the Right Treatment (STOPP/START version 2 criteria), used to detect potentially inappropriate medications and potential prescribing omissions, has been found to improve medication appropriateness, reduce medication costs, reduce falls, and decrease adverse drug events (O'Mahony, 2020; O'Mahony et al., 2015). The criteria recommend stopping any drug prescribed without an evidence-based clinical indication, any drug prescribed beyond the recommended duration, and any concurrent use of more than one SSRI or SNRI. In a review of 15 deprescribing tools

for older adults with multimorbidity, Thompson et al. (2019) concluded that the Screening Tool of Older Persons Prescriptions in Frail Adults with limited life expectancy (STOPPFrail) stepwise approach and algorithm for deprescribing (Lavan et al., 2017) was the most clinically useful tool for older adults with limited life expectancy.

The List of Evidence-Based Deprescribing for Chronic Patients criteria (LESS-CHRON; Rodríguez-Pérez et al., 2017) is a tool that provides guidelines about the appropriate timeline for deprescribing. **Table A** (available in the online version of this article) presents a comparison of the Beers Criteria, STOPP/START, and LESS-CHRON recommendations in regard to psychotropic medications.

IMPLICATIONS FOR PRESCRIBERS

A rational approach to treating older adults with mental health concerns should include knowing where to look for current evidence-based resources. Psychotropics are often prescribed during acute exacerbations of symptoms and during hospitalizations. Those temporary treatments can be deprescribed approximately 1 month post recovery. For older adults who have diagnosable mental disorders, long-term treatment may be indicated. Antipsychotics may continue to be the best treatment for patients with schizophrenia or bipolar disorder. Drugs that have been life-saving for some persons (e.g., lithium) may need to be switched in older age due to the renal effects of aging and of the drug over time. The Beers Criteria (AGS Beers Criteria® Update Expert Panel, 2019), START/STOP Tool (O'Mahony, 2020), and LESS-CHRON (Rodríguez-Pérez et al., 2017) provide guidance in examining potential harms and drugs to be deprescribed. Additional help in deprescribing benzodiazepines can be found at Deprescribing.org. Unfortunately, long lists of medications can be the result of prescribing cascades that occur when an adverse effect of one

medication is treated as a new symptom of a disorder. Evaluating each new symptom as a potential adverse effect is key to preventing medication overload.

When it comes to selecting one drug over another within a class, side effect comparison tables can be used to identify the safest drugs (e.g., UpToDate.com). For older adults who are likely to be on multiple medications, choice of medication will also require preventing clinically relevant potential CYP450 drug–drug interactions. The Flockhart Table™ (also available at Crediblemeds.org) can be easily used to determine if a drug being considered is likely to interfere with the metabolism of other drugs that the patient is already taking. Crediblemeds.org also includes prescriber resources to avoid additive drug effects that increase QTc. These resources make it clear that, of the antidepressants, escitalopram and sertraline are two of the safest choices. Aripiprazole is considered the prototype of a third-generation antipsychotic based on its D2 stabilizing effects through partial agonism. Of all the first-line antipsychotics, it has the lowest risk across all categories of adverse effects.

The AGS Beers Criteria® Update Expert Panel (2019) recommends avoiding a treatment regimen with more than three CNS–active drugs. Reported barriers to the deprescribing process include lack of time, difficulty in communicating and establishing goals of care with older patients and/or caregivers, lack of disease-specific guidelines on discontinuation of certain medications, a focus on symptomatic rather than functional outcomes, concerns about the possible re-emergence of psychiatric symptoms, and concerns about withdrawal (Djatche et al., 2018; Gupta & Cahill, 2016; Reeve et al., 2017). In psychiatry, it is also important to choose the right time to deprescribe, not at times of acute illness or crisis

(Gupta & Cahill, 2016). When deprescribing or prescribing to older adults, it is considered wise to make incremental changes, tapering medications to avoid withdrawal effects and starting new medications low and going slow to avoid side effects and to find the lowest possible therapeutic dose. Because of multimorbidity, the increasing complexity of care, and the risks associated with polypharmacy, collaboration among providers is essential. Integrated care, all under one roof with shared electronic medical records, is best for older adults because it eases the treatment burden; however, this is not always possible. The deprescribing and prescribing process of treating older adults takes on a pattern, as well as a goal, of continuous quality improvement.

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COMPARISON OF RECOMMENDATIONS FOR PSYCHOTROPIC TREATMENT OF OLDER ADULTS

	Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults	STOPP Version 2	START Version 2	LESS-CHRON
Source	American Geriatrics Society Beers Criteria Update Expert Panel (2019)	O'Mahony et al. (2015)	O'Mahony et al. (2015)	Rodríguez-Pérez et al. (2017)
Antidepressants	Avoid tricyclic antidepressants (TCAs) Avoid duloxetine if creatinine clearance (CCR) <30 Avoid if history of falls/fractures	STOP TCAs as first-line antidepressant treatment STOP TCAs with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or history of urinary retention STOP SSRIs with current or recent hyponatremia	START non-TCA antidepressants in the presence of persistent major depressive symptoms START SSRIs for persistent severe anxiety that interferes with independent functioning	Antidepressants that have been prescribed for reactive depression may be deprescribed 6 months after recovery from the episode
Anticholinergics	Avoid highly anticholinergic medications (e.g., hydroxyzine, diphenhydramine)	STOP if treating extra-pyramidal side effects (EPS) of antipsychotics STOP if dementia or delirium is present		
Antiepileptics	Avoid if history of falls/fractures Avoid gabapentin if CCR <60			Antipsychotics that have been prescribed for delirium during hospitalization may be deprescribed 1 month after behavioral stability
Antihistamines		STOP if first-generation drug		

COMPARISON OF RECOMMENDATIONS FOR PSYCHOTROPIC TREATMENT OF OLDER ADULTS

	Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults	STOPP Version 2	START Version 2	LESS-CHRON
Antipsychotics (first- and second-generation)	Avoid if highly anticholinergic Avoid if history of falls/fractures	STOP if marked anticholinergic effects (e.g., clozapine) STOP if history of prostatism or urinary retention STOP in persons with Parkinsonism or Lewy body disease (exceptions: quetiapine or clozapine) STOP if prescribed for sleep disorder (unless due to psychosis)		Antipsychotics that have been prescribed for delirium during hospitalization may be deprescribed 1 month after behavioral stability
Anxiolytics (benzodiazepines and Z-drugs)	Avoid in general Avoid if history of falls/fractures	STOP if taken for ≥4 weeks		Benzodiazepines prescribed for anxiety may be deprescribed 1 month after recovery is reached Benzodiazepines and nonbenzodiazepine receptor agonists prescribed for insomnia may be deprescribed 1 month after recovery is reached
Lithium	Avoid with angiotensin-converting enzyme inhibitors and loop diuretics			

Note. STOP = Screening Tool of Older Person's Potentially Inappropriate Prescriptions; START = Screening Tool of Alert Doctors to the Right Treatment; LESS-CHRON = List of Evidence-Based Deprescribing for Chronic Patients; SSRIs = selective serotonin reuptake inhibitors.