

Review Article

Prescribing Cascade — What, When, How and the Ways to Mitigate

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Rational prescribing is essential for adequate patient compliance and proper therapeutic outcome. Often medicines are prescribed randomly to take care of the drug induced adverse reactions without changing the culprit drug or modifying its dose, rather commonly by adding another drug towards amelioration of the presenting complain, ignoring its drug related occurrence. This 'Prescribing Cascade' turns out to be a vicious cycle by promoting polypharmacy thus leading to its adverse consequences. This can happen to any person at any age but elderly population are more vulnerable because of their age related physiological changes and co-morbidities. There are several ways to curb the vicious cycle down like anticholinergic burden assessment, selecting the right drug for the right person, medication reconciliation etc.

[J Indian Med Assoc 2022; 120(9): 39-43]

Key words : Prescribing cascade, Polypharmacy, Rational prescribing, Pharmacovigilance, Anticholinergic burden, Deprescribing

Let us analyse a case scenario where a middle aged male with Chronic Renal Failure (CRF) receiving high dose ARB (Temisartan 80 mg twice daily and toremide- spironolactone combination once daily develops bradycardia, respiratory distress). ECG revealed features of complete heartblock and he was advised pacemaker implantation. Subsequently he was diagnosed as hyperkalemia in a case of advanced CRF and corrected with dialysis. So, failure to recognise the initial adverse drug reaction encouraged to commute another adventure posing potential physical, mental and of course financial harm.

Prescribing Cascade by definition indicates the use of additional drugs or device to treat an iatrogenic-induced condition by a first drug (Adverse Drug Reaction or ADR) in the wrong idea that this is a different medical event (but not the ADR) requiring obligatory treatment and whose outstanding feature is that it could have been prevented if first drug had been properly used or the ADR recognized¹.

Prescribing cascade is a relatively new term introduced by Rochon and Gurwitz in 1995 to identify a major Geriatric problem². It has immense impact in practice of Medicine, yet not achieved due recognition till date.

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Received on : 31/08/2022

Accepted on : 05/09/2022

Editor's Comment :

- Prescribing cascade often leads to harmful health consequences particularly in the elderly population.
- Rational pharmacotherapy and selective deprescribing are the key measures to prevent its occurrence.
- Add on specialized Clinical Pharmacology service can improve the patient care and treatment outcome across the health care facilities.

Prescribing Cascade can occur in anyone receiving more than one drug therapy, regardless of age but it is more common in older adults because they are more likely to have co-morbidities that require a number of drug therapies (Fig 1).

Examples : Elderly subjects are more prone to develop Anticholinergic adverse drug reactions. There are several drugs which have additional anticholinergic activities and when many drugs are prescribed, their individual anticholinergic activities are summed up leading to overall increased anticholinergic burden (Fig 2).

It is also to be noted that antipsychotic drugs, when used in combination, often land up with increase in side effects by promoting Prescribing Cascade and finally not with standing their purpose to improve efficacy. The cascade occurs in the following order

Cholinesterase Inhibitors like donepezil, rivastigmine are often used for Dementia in elderly persons. These drugs may cause Diarrhoea and Urinary incontinence because of cholinergic side effects. This may perpetuate a Prescribing Cascade upon prescription of an anticholinergic drug like oxybutinin causing urinary retention, dry mouth, constipation etc.

Prescribing Cascade can occur in both elderly and in other age groups. Besides anticholinesterases and

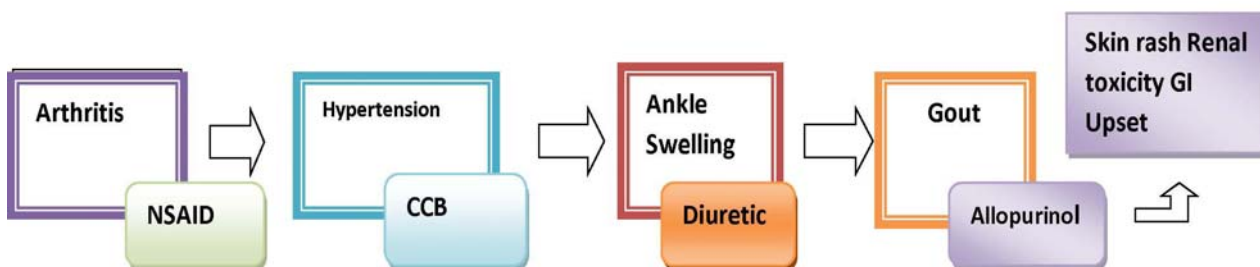


Fig 1 — Prescribing Cascade when many drugs are used in tandem

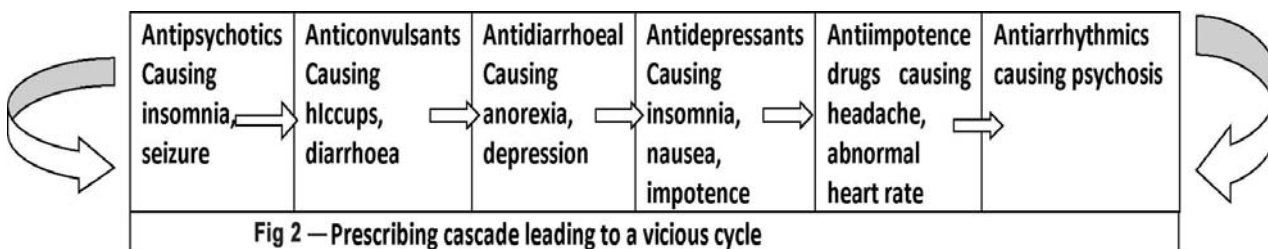


Fig 2 — Prescribing cascade leading to a vicious cycle

antipsychotics, an ample number of medications can lead to prescribing Cascade (Table 1).

Thus Physicians should be aware of the potential adverse effects of the medications they prescribe to recognise ADRs early and take appropriate actions by either withdrawing the medications or reducing the dose.

Anticholinergic Burden :

Anticholinergic drugs are meant to block the neurotransmitter acetylcholine. Anticholinergics have systemic effects on smooth muscle function including the Lungs, Gastrointestinal System and Urinary Tract. These drugs are therefore prescribed in variety of medical conditions including Parkinson’s Disease, Allergies, Chronic Obstructive Pulmonary Disease, Depression and Urinary Incontinence. Some commonly used drugs in elderly like Oxybutynin, Benztropine, Diphenhydramine, Olanzapine and Amitryptiline have substantial anticholinergic properties and should be used in caution and suitable alternatives with less anticholinergic burden are better to be chosen^{4,5} (Table 2) provides a comprehensive list of medications with anticholinergic properties prescribed in elderly.

Adverse Drug Reaction (ADR) with anticholinergic properties :

Common ADRs in this category are dry mouth, blurred vision, constipation, urinary retention, decreased sweating, dry eyes, heat intolerance, tachycardia, dizziness, confusion, delirium, drowsiness, cognitive impairment and fall. The anticholinergic effect increases if highly potent anticholinergics are used, in high dose or in combination. Older patients more likely to have multiple co-morbidities and are on several medications. As the body ages, it’s drug metabolising activity, renal

Table1 — Examples of Prescribing Cascade^{2,3}

Initial treatment	Adverse Effect	Subsequent Treatment	Subsequent adverse event
ACE inhibitors	Dry cough	Anti-histamines	Sedation, increased frequency of fall
Anti-Cholinesterase	Urinary Incontinence	Oxybutynin	Urinary retention, Constipation
NSAIDs	Rise in Blood Pressure	Anti-hypertensive	Dizziness, Orthostatic Hypotension
Thiazide	Hyperuricaemia	Xanthine-oxidase inhibitor (allopurinol, febuxostat)	GI upset, Acute kidney injury, Skin rash
Anti-hypertensives	Dizziness (orthostatic hypotension)	Prochlorperazine	Parkinsonism like features
Statins	Muscle pain	Baclofen	Sedation
Haloperidol	Parkinsonism like features	Procyclidine	Dry mouth, Glaucoma, Retention of urine
Amitryptiline	Prolonged QT interval and arrhythmia	Antiarrhythmics	Further arrhythmia
Tamsulosin	Postural hypotension and dizziness	Vestibular sedatives	Sedation, Increased frequency of falls
Metoclopramide	Parkinsonism like features	Levodopa	Visual and auditory hallucination

Table 2 — Common medications with anticholinergic properties used in the elderly populations*

Medications Used Specifically for their Anticholinergic Properties	Medications With Anticholinergic Properties Unrelated to Their Primary Use
Atropine (GI spasms, sialorrhea)#	Amitriptyline (depression, neuropathic pain)#
Benzotropine (movement disorders)#	Carisoprodol (muscle spasms)#
Darifenacin (overactive bladder)	Chlorpheniramine (allergic rhinitis)#
Dicyclomine (GI spasms)#	Chlorpromazine (agitation, N/V, psychosis) #
Hyoscyamine (GI spasms, sialorrhea)#	Cyclobenzaprine (muscle spasms)
Ipratropium (bronchospasm)	Diphenhydramine (insomnia, pruritus)#
Meclizine (motion sickness, N/V, vertigo)#	Disopyramide (arrhythmias)
Oxybutynin (overactive bladder)#	Doxepin (depression, insomnia)
Scopolamine (motion sickness, N/V, sialorrhea)	Metaxalone (muscle spasms)
Solifenacin (overactive bladder)	Methocarbamol (muscle spasms)
Tiotropium (bronchospasm)	Olanzapine (agitation, psychosis)
Tolterodine (overactive bladder)	Paroxetine (depression, panic disorder)
Trihexyphenidyl (movement disorders)	Procainamide (arrhythmias)
Trimethobenzamide (N/V)	Promethazine (motion sickness, N/V)#
Tropium (overactive bladder)	Quetiapine (agitation, psychosis)

GI = Gastrointestinal, N/V = Nausea/Vomiting, *Uses are provided within bracket.
#Drugs with strong ACh properties Table adapted from reference 6

in routine clinical practice is the use of anticholinergic rating scales. Many such scales are in use^{6,8-10}.

The purpose of the Anticholinergic Burden Calculator is to aid the clinician in their decision making during a medication review and to offer alternative drugs with a lower anticholinergic burden.

The corrective actions include, to avoid the drugs with strong anticholinergic properties in the elderly and if used at all, should be used in lowest possible doses and duration. The anticholinergic burden can be further reduced

clearance are diminished and because of age related dementia older patients are more sensitive to the anticholinergic effects of the medications^{4,5,7}. Thus, assessing anticholinergic burden is mandatory in elderly population.

Moreover, anticholinergic ADRs may be misdiagnosed as clinical presentations due to advancing age or worsening of the existing disease conditions instead of recognising as medication related issues. This can promote prescribing cascade by using medications for the remedy and thus lead to increased medication costs, healthcare expenditures, more bodily harm, lower quality of life of the patients and caregiver burden as well^{5,7}.

Reducing Anticholinergic Burden :

Anticholinergic Burden tables were created in 2008 in an attempt to quantify the effects of these medications, and provide a practical tool for optimising prescribing for older patients⁴. It is worth mentioning that anticholinergic use for long duration and risk of developing cognitive impairment, dementia have been reflected in several research studies^{5,6} (Table 3).

Assessing Anticholinergic Burden :

Anticholinergic burden can be assessed by anticholinergic rating scales and radioreceptor assays. A detailed review of different methods has been published earlier. Currently the useful tools for assessing anticholinergic burden

by replacing medications having strong anticholinergic properties with low potent alternatives, medications without such activities or with behavioural and physical therapies as appropriate.

Deprescribe and Reassess :

The concept of deprescribing is now coming up in a big way. According to Dementia Antipsychotic

Table 3 — Alternatives to medications with strong anticholinergic properties

Medications With Strong Anticholinergic Properties	Alternatives
First-generation antihistamines for allergic rhinitis (eg, chlorpheniramine)	Second-generation antihistamines (eg, cetirizine, loratadine)
First-generation antihistamines for insomnia (eg, diphenhydramine)	Non-pharmacologic interventions (eg, eliminate caffeine, reduce daytime napping), low-dose trazodone, non-benzodiazepine sedative-hypnotic (eg, eszopiclone, zolpidem)
Bladder antispasmodics for overactive bladder (eg, oxybutynin)	Non-pharmacologic interventions (eg, Kegel exercises, scheduled toileting)
Muscle relaxants for muscle spasms (eg, carisoprodol)	Non-pharmacologic interventions (eg, massage, physical therapy) and appropriate pain management (eg, acetaminophen, oxycodone)
TCAs for depression (eg, amitriptyline)	SSRI antidepressants (eg, citalopram, sertraline), SNRI antidepressants (eg, duloxetine, venlafaxine), TCAs with weak ACh properties (eg, nortriptyline)
TCAs for insomnia (eg, doxepin)	Non-pharmacologic interventions (eg, eliminate caffeine, reduce daytime napping), low-dose trazodone, non-benzodiazepine sedative-hypnotic (eg, eszopiclone, zolpidem)
TCAs for neuropathic pain (eg, amitriptyline)	Gabapentin, TCAs with weak ACh properties (eg, nortriptyline)

SNRI = Serotonin-Norepinephrine Reuptake Inhibitor, SSRI = Selective Serotonin Reuptake Inhibitor, TCAs = Tricyclic Antidepressants. Table adapted from reference 6

Withdrawal Trial (DART-AD), 2009, significantly less number of patients died with deprescribed medications (antipsychotics) at 1 to 3 years follow-up than those without deprescribing¹¹. In another study some medications were selectively deprescribed from 120 elderly patients following 'Geriatric palliative deprescribing algorithm' like nitrates (in case no chest pain), H₂ blockers (without gastrointestinal bleed), and antihypertensives (among many prescribed). In comparison with a age, gender and comorbidity matched control group sans deprescribing, the deprescription group had reduced 1-year death rate (21% *versus* 45%) and substantial reduction in referral to Emergency Medicine Departments over 1 year (12% *versus* 30%), revealing highly significant differences¹².

Truly speaking, deprescribing is not a once and final action. The scope for drug discontinuation should be periodically assessed in long term care settings with regular monitoring of patients for adverse effects. Several barriers to deprescribing also exist. Care providers often feel shaky to change the drugs prescribed by other physicians and patients are also often very much attached to the drugs and their regular physicians. This emphasises the need for patient-education and proper communication by the healthcare professionals. Additionally they need to recognise the evils of prescribing cascade and the benefits of deprescribing. Though a less talked area, deprescribing is now an internationally recognised term and this concept is growing very fast.

Pedal edema is a common side effect of amlodipine which is often unnecessarily treated with diuretic like furosemide or thiazide. To counteract the assumed urinary incontinence in this patient, tolterodine is often prescribed promoting dry mouth for which anetholtrithion, a drug to stimulate salivary secretions is prescribed making a case of prescribing cascade¹³. These practice of over prescribing without recognising the root cause of the problem merely increases the pill burden and consequent fatalities. These ventures should be discouraged and the scope of drug discontinuation and replacement with safer alternatives should be reassessed periodically in the long term care settings. This can be done in consultation with a Clinical Pharmacologist when available.

An unrecognised adverse drug reaction can be unfolded further by the consequent prescribing cascade. An Australian veterans study revealed increased rate of prochlorperazine prescription in cases of dizziness caused by prescription drugs like antihypertensives. However, prochlorperazine leads to further exacerbation of dizziness by causing postural hypotension. Thus a prescribing cascade may cause

increased morbidity and mortality due to increased rate of fall leading to hip fracture and hospitalisation¹⁴.

Prescribing Cascade and Pharmacovigilance :

Different factors are responsible for Adverse Drug Reactions (ADR) eg, taking multiple or inappropriate medications, altered pharmacokinetics and pharmacodynamics associated with aging, female gender and having genetic factors, sustaining multiple co-existing medical problems and having cognitive issues. ADR are often misunderstood and lead to a huge economic, ethical and legal burden to the society. Thus proper understanding of the concept of pharmacovigilance and developing an insight for prevention, detection, reporting and monitoring of ADR is utmost necessary for the Healthcare Professionals. The patients should also be sensitized and made aware to recognise any bodily abnormality and bring it to the knowledge of the physician at the earliest. In India, Pharmacovigilance Programme of India (PvPI) has been functioning for many years. So every Healthcare Professional and even public should make use of it by timely reporting the suspected ADRs, enriching database, facilitating signal generation for unknown ADRs and propagating the message for wider circulation. If we strengthen our Pharmacovigilance activities it will indirectly decrease the occurrence of prescribing cascade with increased awareness and vigilance about suspected ADRs facilitating corrective actions to be taken at the earliest.

Recommendations for better prescribing and research activities to prevent prescribing cascade :¹⁵

(1) To prevent prescribing cascade consider starting drug therapies of lower initial doses, selecting drugs with fewer side effects,

(2) Initiation of a reconciliation process by separate caregivers (Clinical Pharmacology Service), by actively interviewing the patients whether a new drug is being used to treat a side effect from another drug they are taking.

(3) Take the help of several case studies and tools to detect prescribing cascade.

(4) To reverse prescribing cascade conduct a medication review and dose tapering or discontinuation if feasible.

(5) To identify clinically important prescribing cascades there is a need to do research on health database and patient data sources. Electronic prescribing and record keeping is highly recommended for this purpose.

(6) The effect of such prescribing cascades on Healthcare system should be evaluated for designing appropriate policies and using tools to reduce them.

(7) There is a need to do intervention studies to assess the efficacy of decision making tools and guidelines in clinical practice.

Prescribing is a continuous process which spans from the decision to prescribe to stopping the medication in the context of medical care. In this continuum of care there are every opportunity to review the drug therapy and the prescribers should be aware of the possibility of prescribing cascade, the commonly occurring ones, their clinical presentation and interventions available to reduce the prevalence. Actually prevention of prescribing cascade starts even before the act of prescribing and continues during prescribing while detection can be done during prescribing, reviewing medications or even during population research. Reversal of prescribing cascade is the shared responsibility of the prescriber and the patients even after detection. There are several tools to assist prescribing cascade detection like algorithms, protocols, check lists and even mobile based software applications. Studies revealed their good acceptance and efficacy in changing prescriber's behaviour by reducing medication burden in individuals. These tools are easy to be implemented in clinical practice to reduce prescribing cascade and polypharmacy.

Conclusion :

Prescribing cascade is an universally recognised issue. Being informed from the range of resources this review is intended to percolate this message to prevent, identify, and rectify prescribing cascades and find the ways to implement the same with an ultimate goal to improve drug prescribing. We all know that many commonly used medications by elderly patients results in cumulative high anticholinergic effect often leading to catastrophic health hazards. Firstly, those medications should be avoided at best in elderly subjects but some are used specifically for the anticholinergic activities, rendering the withdrawal decision more challenging. Treating physicians need to be well informed, vigilant and should utilize the anticholinergic rating scales to assess the anticholinergic burden while prescribing to foster better medication safety among elderly patients.

As deprescribing initiatives are on rise, it is assumed that raising awareness about the prescribing cascade concept and methods and modalities to detect, deprescribe and reverse the same will grow and attract attention within medical fraternity and patient population as well. The importance of a specialised Clinical Pharmacology Service by the supervision of a Clinical Pharmacologist is being recognised globally and is the need of the hour even

in a country like India. However, in spite of it's huge potential impact on patients' health and quality of life, still it is a less traversed area by the clinicians and researchers even today. As highlighted in this article, different physicians including Clinical Pharmacologists should keep their hands together in the identification, monitoring and resolution of prescribing cascades and taking measures to prevent it's future occurrence in their respective patient care arenas. We also need focused research on prescribing cascade and generate epidemiological data to explore the possible reasons or factors determining this specific problem.

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