Medication and Substance-Induced Cognitive Impairment

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Objectives

1.) Review some of the presentations of cognitive impairment that may be caused by medications or other substances

2.) Understand the common medications or substances that can contribute to cognitive impairment

3.) Develop an approach to managing individual with substance induced cognitive impairment

When do you think about substances playing a role in cognitive impairment?

- Younger individuals
- Onset of symptoms corresponding with initiation of medication or change in dosage
  - Change in metabolism/clearance
- "Neurological signs" – lethargy, falls, coordination problems
- Non-progressive cognitive impairment
- Fluctuating performance
- Polypharmacy
- High-risk medications
- History of substance misuse

Medications and Substance that May Impact Cognition

- Anticholinergic medications
  - Anticholinergic Risk Scale – better at predicting ADL impairment
  - Anticholinergic Cognitive Burden Scale – better at predicting cognition
  - Anticholinergic Burden Scale
- Sedative + Anticholinergic Medications
  - Drug Burden Index (DBI)
- Substances
  - Alcohol
  - Cannabis

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Anticholinergic Risk Scale

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Score = 3 points	Score = 2 points	Score = 1 point
Amitriptyline	Amantadine	Carbidopa-levodopa
Atropine products	Hydrochloride	
Benztropine	Baclofen	Entacapone
Carisoprodol	Cetirizine	Haloperidol
Chlorpheniramine	Cimetidine	Methocarbamol
Chlorpromazine	Clozapine	Metoclopramide
Cyproheptadine		Mirtazapine
Dicyclomine	Cyclobenzaprine	
Diphenhydramine	Hydrochloride	
Fluphenazine	Desipramine	Paroxetine
Hydroxyzine hydrochloride &	Loperamide	Pramipexole
hydroxyzine pamoate	Loratadine	Quetiapine fumarate
Hyoscyamine products		
	Nortriptyline	
Imipramine	Olanzapine	Ranitidine
		Risperidone
Meclizine		
	Prochlorperazine	
Oxybutynin	Pseudoephedrine &	Selegiline
Perphenazine	Triprolidine	Trazodone
Promethazine	Tolterodine tartrate	
Thioridazine		Ziprasidone
Thiothixene		
Tizanidine		
Trifluoperazine		

Anticholinergic Cognitive Burden

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Drugs with ACB Score of 1

Generic Name	Brand Name
Alimemazine	Theralen™
Alverine	Spasmonal™
Alprazolam	Xanax™
Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Nefopam	Nefogesic™
Oxcarbazepine	Trileptal™
Pimozide	Orap™

Categorical Scoring:

- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

Aging Brain Care

www.agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Anticholinergics and Dementia

- Cumulative exposure to highly anticholinergic medications associated with an increased risk of dementia with higher doses of anticholinergics
  - HR: 1.23 for moderate exposure, HR: 1.5 for high exposure
- Anticholinergic medications associated with increased risk of dementia
  - OR: 1.1, increasing score increased risk
  - Antidepressant, antiparkinsonian and urological ACB had highest risk

Gray, JAMA Int Med, 2015
Richardson, BMJ, 2018

Drug Burden Index

- Both anticholinergic and sedative medications can have an impact on cognition and functioning
- Drug Burden Index quantifies the total cognitive load of all the medications prescribed to an individual

Drug Burden Index

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SupplementaryTable S1. Master Drug Burden Index (DBI) list - medications for inclusion in the calculation of DBI

Drug	WHO ATC Code/s	Anticholinergic effects (AC)	Sedative effects (S)	Minimum effective daily dose by route of administration (mg)					
				Oral	Parenteral	Sublingual/buccal	Transdermal	Rectal	Inhalation
Alimemazine	R06AD01	AC	S	10					
Alprazolam	N05BA12		S	0.5					
Amantadine	N04BB01	AC		100					
Amisulpride	N05AL05		S	50					
Amitriptyline	N06AA09	AC	S	10					
Aripiprazole	N05AX12		S	10	10				
Asenapine	N05AH05		S			10			
Atropine	A03BA01 AO3CB03	AC		0.6	0.3				
Baclofen	M03BX01		S	30	30				
Benperidol	N05AD07		S	0.125					
Benzatropine	N04AC01	AC		0.5	0.5				
Biperiden	N04AA02	AC	S	1					
Brompheniramine	R06AB01 R06AB51	AC	S	16					
Buclizine	R06AE51 R06AE01	AC	S	12.5					
Buprenorphine	N02AE01		S		0.12	0.4	0.12		
Buspirone	N05BE01		S	15					
Carbamazepine	N03AF01	AC	S	400				500	
Cetirizine	R06AE07		S	10					
Cloral Hydrate	N05CC01		S	430					
Chlordiazepoxide	N05BA02		S	5					
Chlorphenamine	R06AB04	AC	S	8	3				
Chlorpromazine	N05AA01	AC	S	30	6				
Cinnarizine	N07CA02	AC	S	60					

Medications in DBI

- Antihistamines (H1 antihistamines)
- Anticholinergics (bladder and others)
- Antidepressants
- Benzodiazepines
- Z-drugs
- Antipsychotics
- Anticonvulsants
- Opioid narcotics

Calculating DBI

- Contribution of Medication to DBI for each medication on DBI list
- Example
  - DBI = D(prescribed)/D(prescribed + minimum effective dose)
  - DBI(Clonazepam) = D(2 mg)/(2mg + 0.5)
  - DBI (Clonazepam) = 0.8
  - DBI(Clonazepam) 0.8 + DBI(Amitriptyline) 0.71 + DBI(Gravol)0.4 + DBI(Tramacet)0.42 = DBI(total) = 2.31

Drug Burden Index and Outcomes

- 2/3 of population exposed to at least one DBI medication
- Increasing DBI (DBI score ≥ 1) associated with a number of adverse outcomes
  - Increased mortality
  - Falls
  - Functional decline
  - Cognitive impairment
  - Decreased quality of life

Bryne, BMJ Open, 2018
Wouters, Eur J Clin Pharmacol, 2017

Risk of Dementia or Progressive Cognitive Impairment

- Users of anti-Ach drugs have worse cognitive performance compared to non-users
- 80% of individuals using highly anticholinergic drug were characterized as having mild cognitive impairment vs 35% of those on no medications
  - OR: 5 for anticholinergic medications and MCI
- No increased risk of dementia observed in population in association with anti-Ach medications
- DBI scores associated with lower MMSE scores but not with changes in cognition over time

Ancelin, BMJ, 2006; Jamsen, Ann Medicine, 2017

Substance-Induced Cognitive Disorders

- 30% to 80% of individuals with substance use disorders have cognitive impairment meeting criteria for mild cognitive impairment
- Most substances of abuse can impair cognition outside of periods of intoxication
- Persistent cognitive impairment (after prolonged abstinence) can occur, particularly in older adults

Alcohol and Cognition

- Chronic heavy alcohol use can impair cognition
  - Wernicke's encephalopathy untreated 80% → Korsakoff's
- 80% of individuals with alcohol use disorder will have some degree of cognitive impairment
  - Executive dysfunction
- Heavy alcohol consumption associated with 2X increased risk of dementia
  - Unclear if this is direct effect of alcohol or secondary to other complications
- 10 – 20% of dementias may have a contribution of alcohol, particularly in younger age groups

Alcohol and Cognition

- How much alcohol intake is required to potentially cause persistent cognitive deficits?
  - 35 units weekly (280 g) for men
  - 28 units weekly (224 g) for women
- Consumption of > 30 units weekly associated with 5X greater risk of hippocampal atrophy, 14 – 21 units associated with 3X increased risk of atrophy
- Alcohol use guidelines for older adults (CCSMH)
  - Men – no more than 1 – 2 drinks/day and less than 7 per week
  - Women – no more than 1/day and 5 per week
  - Days of no drinking each week

Topiwala, BMJ, 2017

Cannabis and Cognition

- Cannabis can have persistent effects on cognition in adults aside from acute effects
  - Global cognition = ES = -0.29
  - Executive functioning = -0.21
  - Attention =-0.36
  - Learning = -0.35
  - Forgetting =-0.25
  - Language = -0.23
- No differences in cognition between former users and non-users after 1 month of abstinence

Duperrouzel et al, J Dual Diag, 2020

General Approach to Deprescribing

- Remember that medications may cause illness – including ones you may not be aware of!
- Know the patient and their medications – how they are taken, compliance aids
- Consider nonpharmacological therapy
- Know pharmacology (pharmacokinetic/pharmacodynamics) of drugs
- Keep prescribing simple

- Establish treatment goals before starting
- Diagnose prior to prescribing, stop if goals are not met
- Consider existing medications and medical conditions prior to starting new meds
- Start low, go slow (but go!)
- Monitor carefully when starting, stopping medications
- Manage the whole of treatment regimen – communicate with other prescribers

Frank, CMAJ, 2014

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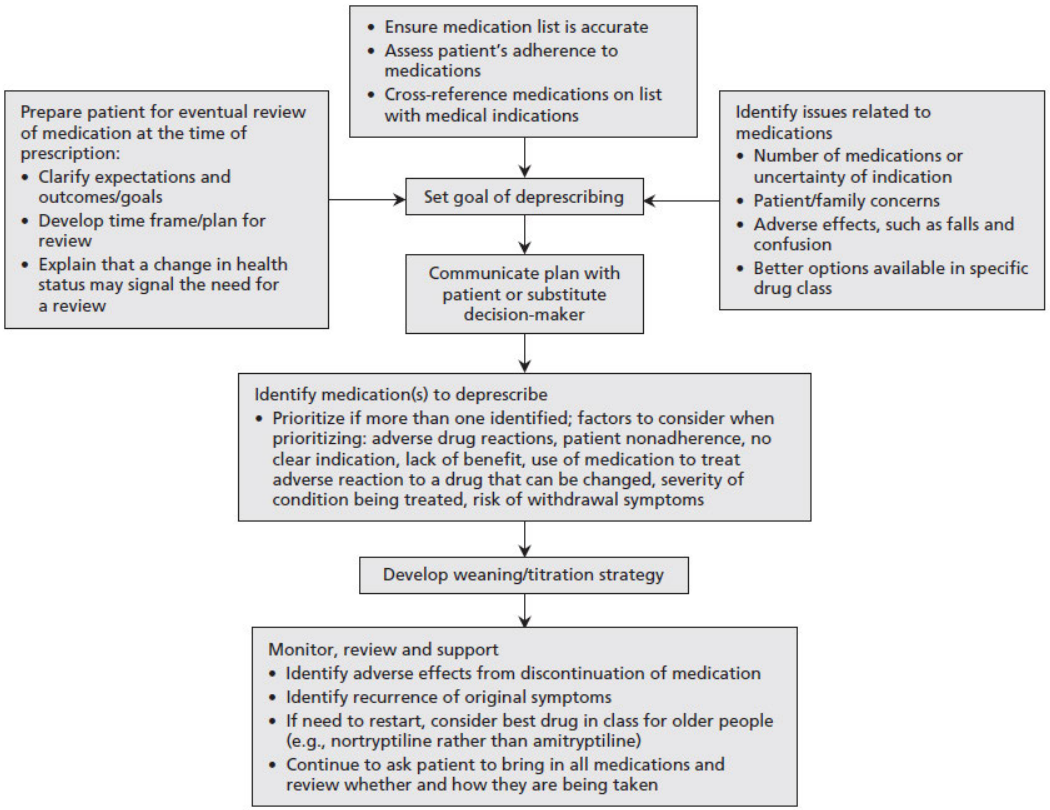
Approach To Deprescribing



Frank, CMAJ, 2014

Screening Tool To Alert Right Treatment (START)

1. Non-TCA antidepressant for persistent major depressive symptoms.

2. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).

3. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.

O'Mahony, Age Ageing, 2015

Screening Tool of Older People's Prescriptions (STOPP)

1. TCAs with dementia, glaucoma, cardiac conduction abnormalities, prostatism, urinary retention
2. Initiation TCAs as first-line antidepressant treatment
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects
4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia
5. Benzodiazepines for ≥ 4 weeks
6. Antipsychotics (other than quetiapine or clozapine) with parkinsonism or Lewy Body Disease
7. Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications
8. Anticholinergics in patients with delirium or dementia
9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil
12. Phenothiazines as first-line treatment for psychiatric symptoms

O'Mahony, Age Aging, 2015

Choosing Wisely Canada

Psychiatry

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5. Don't routinely use antipsychotics to treat primary insomnia in any age group.

7. Don't routinely use antidepressants as first-line treatment for mild or subsyndromal depressive symptoms in adults.

9. Don't routinely continue benzodiazepines initiated during an acute care hospital admission without a careful review and plan of tapering and discontinuing, ideally prior to hospital discharge.

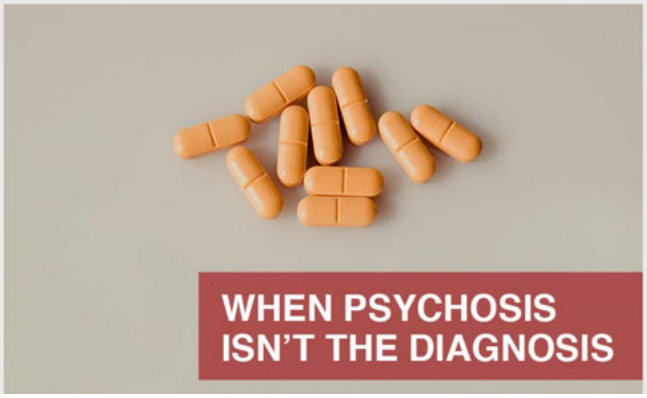
11. Don't routinely prescribe high-dose or combination antipsychotic treatment strategies in the treatment of schizophrenia.

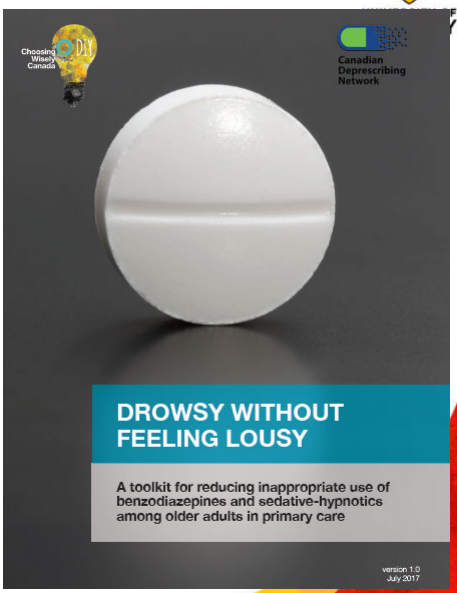
12. Don't use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.

13. Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia.

www.choosingwiselycanada.org

Toolkit: When Psychosis Isn't the Diagnosis





www.choosingwiselycanada.org

Canadian Substance Use Disorders Guidelines

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- Canadian Coalition for Seniors' Mental Health (www.ccsmh.ca)
- Guidelines and Resources on:
  - Alcohol Use Disorder
  - Cannabis Use Disorder
  - Benzodiazepine Use Disorder
  - Opioid Use Disorder