The Dark Side of Psychopharmacology

Managing Common Side Effects of Psychiatric Medications

2018 SCPMG Psychiatry Symposium

The interventions discussed in this talk not FDA-approved for these uses unless specified

Rajnish ("Raj") Mago, MD

Editor-in-Chief
SimpleandPractical.com

Clinical Assistant Professor
University of Pennsylvania
Philadelphia, PA

Learning Objectives

1. Choose medications according to risk profiles
2. Pro-actively manage common side effects with patients.

But wait!

- Great majority are NUISANCE side effects rather than MEDICALLY serious
- Also, many that lead to discontinuation SUBSIDE after 2 to 4 weeks

Call to action!

For each adverse effect – a menu of options

Non-pharmacological or pharmacological

Level 1, Level 2, Level 3

Nausea

Nausea: PDR (≥ 2 X placebo)

> 30%	Divalproex ER 48%, Venlafaxine 31%
> 20%	Paroxetine 26%, Vortioxetine 26%, Sertraline 25%, Vilazodone 23%, Bupropion 22%, Fluoxetine 22%, Atomoxetine 21%, Citalopram 21%
> 10%	Escitalopram 15%, Modafinil 11%, Risperidone 11%
> 5%	Lamotrigine 7%, Mixed amphetamine salts 7%, Lisdexamfetamine 6%

Nausea: Level 2

Example:

Ginger root 550 mg capsules

One or two capsules three times a day

Giacosa et al. (2015). PMID: 25912592
Marx et al. (2015). PMID: 25872115

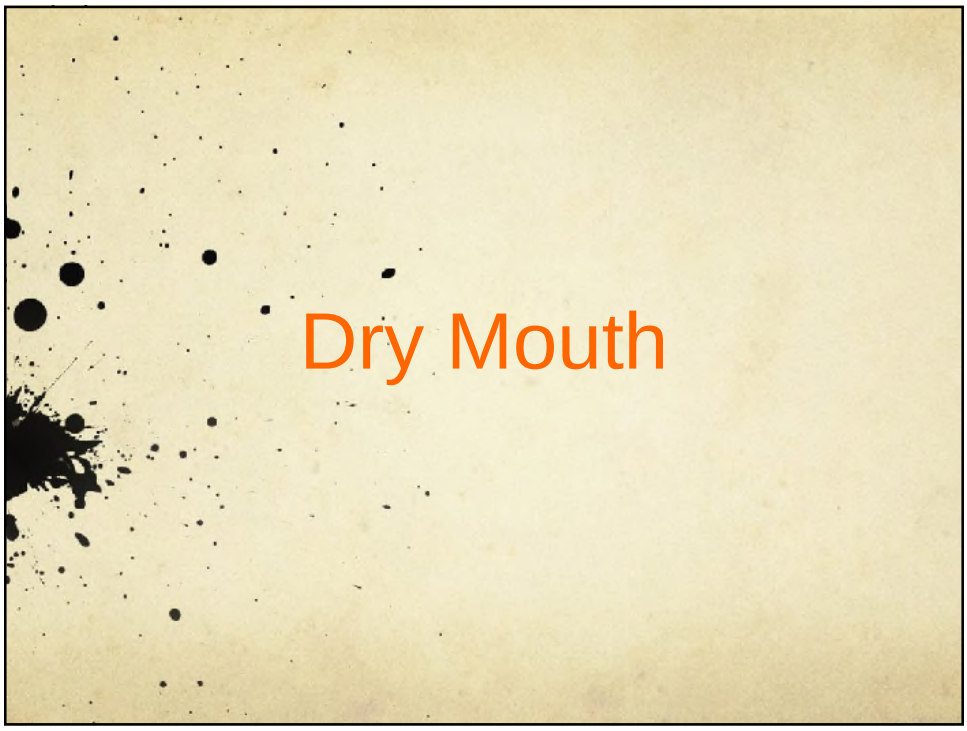
Nausea: Level 3

Antinausea medications

Examples:

- Ondansetron (ODT)

Pedersen & Klysner (1997). PMID: 9179636



Dry Mouth: Why is it important?

- May cause dental caries, oral ulcers
- Persons with mental disorders are:

  - more likely to have caries

  - three times more likely to loose all their teeth

Bardow et al. (2001). PMID: 11286806. Cockburn et al. (2017). PMID: 28759866
Fratto & Manzo (2014). PMID: 25492713. Kisely (2016). PMID: 27254802
Rindal et al. (2005). PMID: 15642049

Management: Level 2

1. Saliva substitutes/oral moisturizers like cellulose gum, glycerin, etc.

Available as gel, oral rinse, gum, toothpaste, etc.

Jose et al. (2017). PMID: 28657703
Mouly et al. (2007). PMID: 17873673
Aliko et al. (2012). PMID: 21898068

Dry mouth: Level 2 (contd.)

2. Xylitol-containing chewing gum

Dry mouth: Level 3

Medication to stimulate saliva production

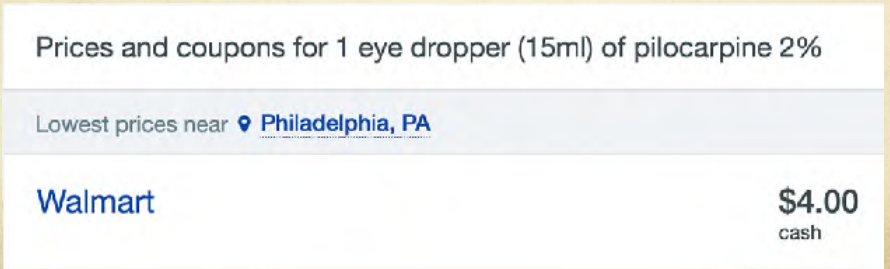
Example: Pilocarpine

Masters (2005). PMID: 15863819
Salah & Cameron (1996). PMID: 8599415

Dry mouth: Level 3

Prefer LOCALLY acting medication

Pilocarpine eye drops



Antidepressant-Induced Excessive Sweating (ADIES)

SA-Q#1. Which of the following medications does not usually cause antidepressant-induced excessive sweating?

A. Bupropion

B. Sertraline

C. Venlafaxine

D. None of the above

PDR (≥ 2 X placebo)

≥ 20%	Bupropion 22%
≥ 10%	Venlafaxine 14%, Citalopram 11%, Paroxetine 11%
≥ 5%	Levomilnacipran 9%, Fluoxetine 8%, Sertraline 8%, Duloxetine 6%, Escitalopram 5%,
< 5%	Atomoxetine 4%, Lisdexamfetamine 3%, Modafinil 1%, Buspirone 1%

Management?

- Wait-and-watch?
- Change antidepressant?

  If feasible, from bupropion or an SNRI to an SSRI (other than paroxetine)

Antidotes?

1. Glycopyrrolate:

Anticholinergic that does not cross the blood-brain barrier to a significant extent

2. Terazosin: alpha blocker

Can cause orthostatic hypotension

Mago et al. (2013). *Ann Clin Psychiatry*. PMID: 23638448.
Mago (2013). *J Clin Psychopharmacol*. PMID: 23422382.

(SA-Q#1) Which of the following medications does not usually cause antidepressant-induced excessive sweating?

A. Bupropion

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Orthostatic Hypotension

SA-Q#2. When going from a lying or sitting position to standing for one to three minutes, what degree of drop in systolic blood pressure is considered to indicate orthostatic hypotension and is correlated with the risk of falling?

A. ≥5 mm Hg

B. ≥10 mm Hg

C. ≥20 mm Hg

D. ≥30 mm Hg

Measure orthostatic BP and pulse

1. After lying (or sitting) down for a few minutes

2. After standing for two minutes”

Drop in SBP of ≥ 20 mmHg

Usually with increase in pulse

Orthostatic hypotension: Level 2

Example:

Venous compression – abdomen, legs

Smeenk et al. (2014). *Neth J Med.* PMID: 24659590
Figueroa et al. (2010). *Cleve Clin J Med.* PMID: 20439562

Venous compression–abdominal binders

Orthostatic hypotension: Level 3

1. Fludrocortisone??
2. Midodrine??
3. Increase salt intake

Figueroa et al. (2010). PMID: 20439562
Gugger (2011). PMID: 21790209
Testani (1994). PMID: 7989286

(SA-Q#2) When going from a lying or sitting position to standing for one to three minutes, what degree of drop in systolic blood pressure is considered to indicate orthostatic hypotension and is correlated with the risk of falling?

A. 5 mm Hg or more

B. 10 mm Hg or more

C. 20 mm Hg or more

D. 30 mm Hg or more

Tremors

Why is this important?

- One of the leading causes of discontinuation of medications like lithium
- Why?
- Socially-embarrassing

Mago et al. (2014). *Harv Rev Psychiatry. PMID: 25377611*

Tremor:
PDR (≥ 2 X placebo)

> 20%	Lithium, Divalproex 25%, Bupropion 21%
> 5%	SSRIs 8%, Olanzapine 6%, Aripiprazole 6%
< 5%	Lamotrigine 4%, Vilazodone 2%, Quetiapine 2%, Buspirone 1%

Tremor: How to monitor?

Tremors: Level 1

1. Reduce caffeine (but caution with lithium)
2. Sustained-release preparations
3. Take medication at bedtime (peak during sleep)

dlfjdsfd

Tremors: Level 2

1. **Antipsychotic-induced tremor**:

   Anticholinergics (e.g., benztropine 2 to 6 mg/day) or amantadine

2. **Lithium-induced tremor**:

   Beta-blocker – does not have to be centrally-acting

Akathisia

SA-Q#3. Which of the following medications may treat akathisia by blocking 5-HT2A receptors?

A. Propranolol

B. Atenolol

C. Mirtazapine

D. Benztropine

Incidence

Ziprasidone	16%
Cariprazine	16%
Aripiprazole	13%
Brexpiprazole?	4-7%
Risperidone	8%
Olanzapine	6%
Quetiapine	4%

Akathisia: Level 1

- Identify!
- How can we prevent akathisia with high-risk medications?

  Titrate up slowly

  Increase in dose of the antipsychotic in the first few days is a risk factor

Miller & Fleischhacker (2000). Drug Safety. PubMed PMID: 10647977.

Akathisia: Level 3

NOT anticholinergics

1. Propranolol

NOT beta-blockers that do not cross the blood-brain barrier and/or are cardioselective

Rathbone & Soares-Weiser (2006). *Cochrane Database Syst Rev*. PMID: 17054182
Lima et al. (2004). *Cochrane Database Syst Rev*. PMID: 15495022

Akathisia: Level 3

2. Clonazepam

3. Mirtazapine (a 5-HT2A antagonist)

Important: Not more than 15 mg/day

Praharaj et al. (2015). *Ther Adv Psychopharmacol.* PMID: 26557987
Poyurovsky et al. (2006). *Biol Psychiatry.* PMID: 16497273.
Laoutidis & Luckhaus (2014). *Int J Neuropsychopharmacol.* PMID: 24286228

(SA-Q#3) Which of the following medications may treat akathisia by blocking 5-HT2A receptors?

A. Propranolol

B. Atenolol

C. Mirtazapine

D. Benztropine

Sexual Dysfunction

SA-Q#4. Which of the following medications has been shown to be effective for the treatment of antidepressant-induced sexual dysfunction?

A. Ginkgo biloba

B. Bupropion

C. Mirtazapine

D. None of the above

Management of ADISD

1. Wait and watch
2. Reduce dose
3. Drug holidays
4. Switch to another antidepressant
5. Add an “antidote”

1. Wait-and-Watch?

- We are overdoing this!
- Even after waiting for 6 to 18 months,

  only **10%** have full improvement and another **10%** have partial improvement

Montejo-Gonzalez et al. (1997). *J Sex Marital Ther.* PMID: 9292833.
Montejo Al et al. (2001). *J Clin Psychiatry*. PMID 11229449.
Ashton & Rosen (1998). *J Sex Martial Ther*. PMID: 9670123
Zajecka (2001). *J Clin Psychiatry*. PMID: 11229451.

3. Drug Holidays?

- Effective for sertraline & paroxetine in 50%
- Not for fluoxetine

Rothschild (1995). *Am J Psychiatry*. PMID: 7573593.

4. Switch to another antidepressant

- **Absent or very low:** Bupropion, Mirtazapine
  Transdermal selegeline
  Moclobemide
- **Lower** Vilazodone
- **High** SSRIs, Duloxetine, Vortioxetine
- **Higher:** Paroxetine, Venlafaxine

5. Add an antidote: Bupropion?

- All three small RCTs done in the US were negative

Masand et al. (2001). *Am J Psychiatry*. PMID: 11329407.
Clayton et al. (2004). *J Clin Psychiatry*. PMID: 14744170.
DeBattista et al. (2005). *J Clin Psychiatry*. PMID: 16013899.

So, should we add bupropion?

1. Would be MUCH better if we could SWITCH to it rather than to add it
2. Consider if:

   - patient is still depressed, or

   - problem is mainly with <u>desire</u>

Add Sildenafil?

- RCTs positive
- 55% improved on sildenafil vs. 4% on placebo

Fava et al. (2006). *J Clin Psychiatry*. PMID:16566619.
Nurnberg et al. (2013). *JAMA.* PMID: 12503977.

Add Testosterone Gel?

- More efficacious than placebo gel in men and women
- In most cases, check level. If low/ low normal, refer to specialist for treatment

Amiaz et al. (2011) *J Sex Marital Ther*. PMID: 21707327.
Fooladi et al. (2014). *J Sex Med*. PMID: PMID: 24433574.

(SA-Q#4) Which of the following medications has been shown to be effective for the treatment of antidepressant-induced sexual dysfunction?

A. Ginkgo biloba

B. Bupropion

C. Mirtazapine

D. None of the above

SA-Q#5. For which of the following potential adverse effects of second-generation antipsychotics, is metformin a potential treatment?

A. Weight gain

B. Akathisia

C. Tardive dyskinesia

D. Hypoglycemia

Weight Gain

Treatment of weight gain

1. Metformin ER 1000 to 2000 mg/day
2. Topiramate 100 to 300 mg/day
3. Amantadine 100 to 400 mg/day
4. Melatonin 5 mg/day

De Hert et al. (2012). *CNS Drugs*. PMID: 22900950.

(SA-Q#5) For which of the following potential adverse effects of second-generation antipsychotics, is metformin a potential treatment?

A. Weight gain

B. Akathisia

C. Tardive dyskinesia

D. Hypoglycemia

Call to action!

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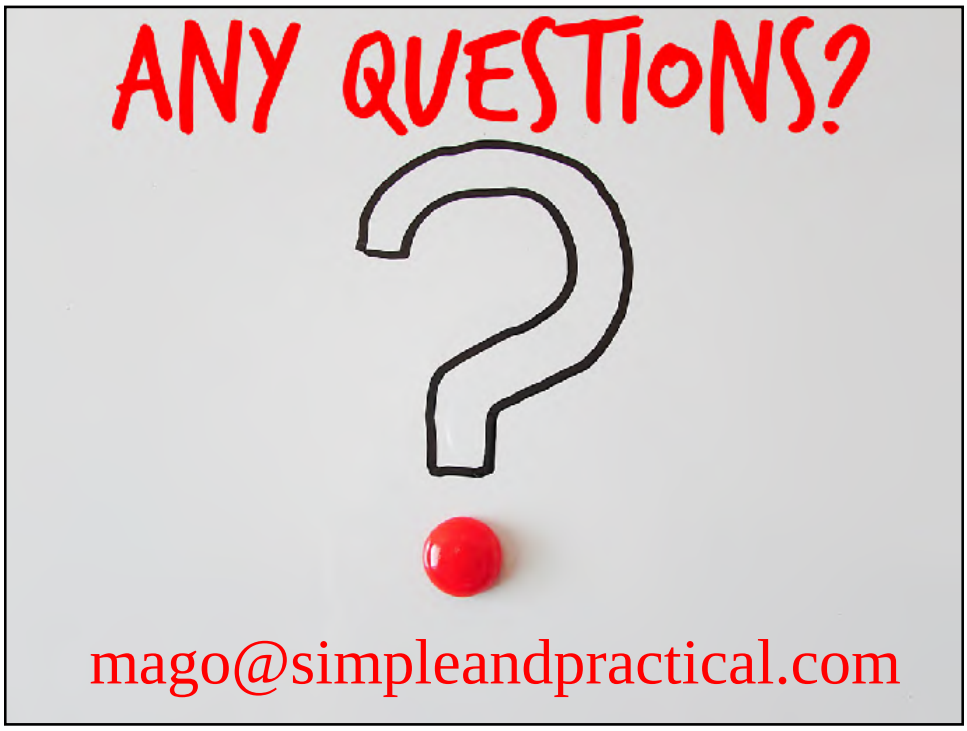

mago@simpleandpractical.com