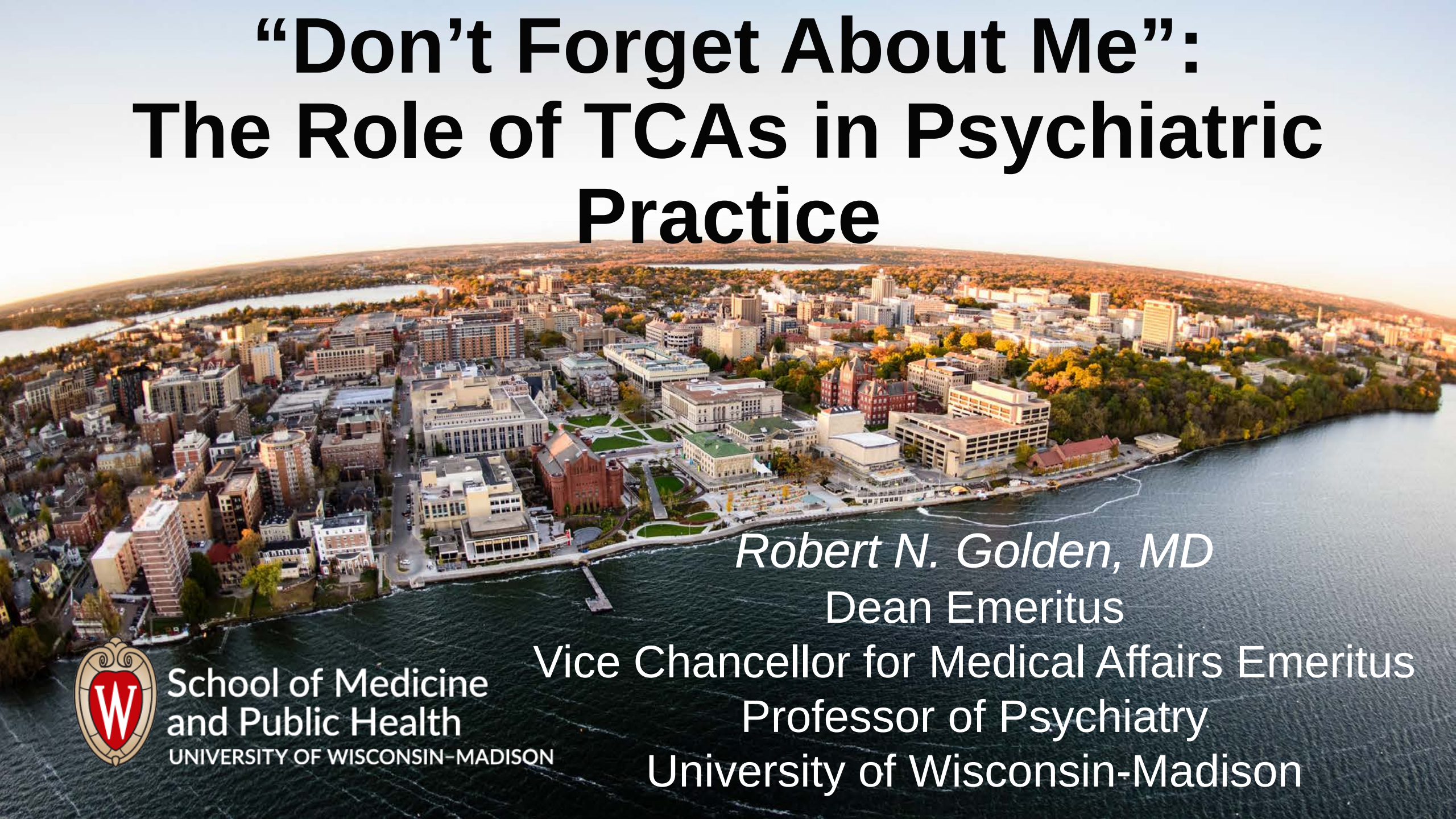
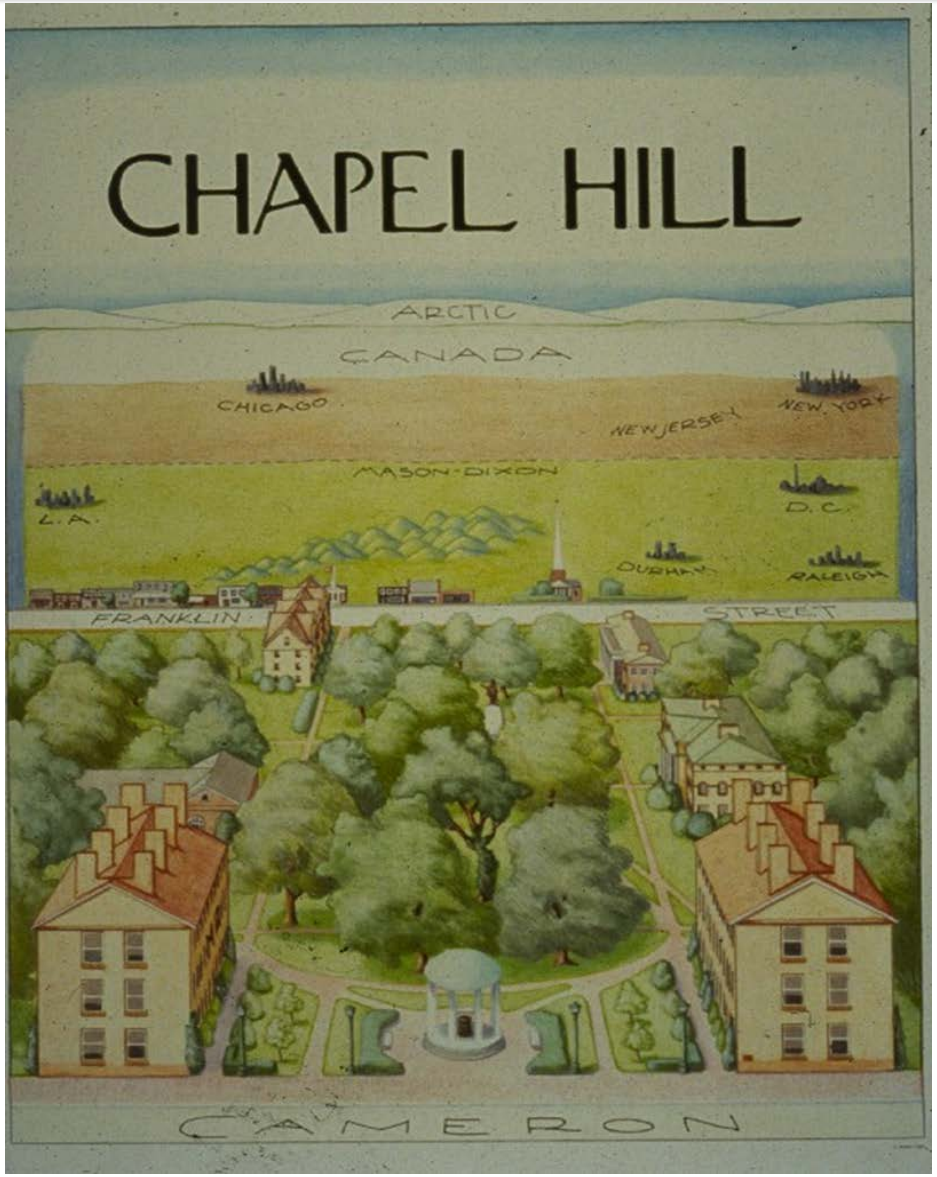
“Don’t Forget About Me”: The Role of TCAs in Psychiatric Practice



Robert N. Golden, MD
Dean Emeritus
Vice Chancellor for Medical Affairs Emeritus
Professor of Psychiatry
University of Wisconsin-Madison

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

Thomas Wolfe was wrong:
You CAN go home again…



Disclaimers/Attestations

- Dr. Golden does not receive any outside compensation (although he does clip discount coupons for Metro Mart grocery shopping).

- The material expressed here today does not in any way reflect the Wisconsin state government…

  ...it is based on data and logic.

Overview

- **History of TCA development and use**
- **TCA Pharmacology**
  - **Structure/function relationships**
  - **Pharmacokinetics**
  - **Pharmacodynamics**
  - **Side effects and Toxicity**.
- **Indications, Efficacy, and Clinical Use**
- **A Simple Way Forward**

History of TCA Development

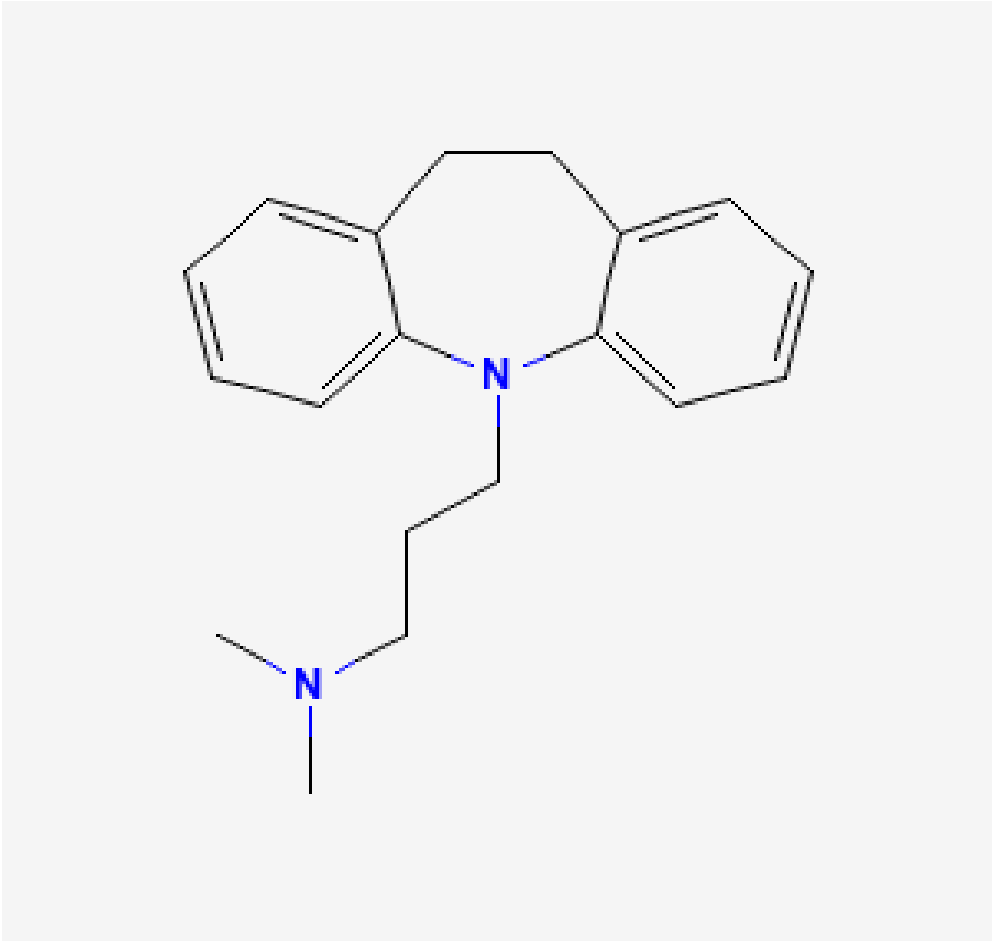
- 1957: Roland Kuhn was looking for an effective sedative.
  - Imipramine: not effective as a sedative, but observed symptomatic relief in depressed patients
- 1960's: Multiple TCAs developed and approved
  - Widespread use
    - 3 biological treatment options: ECT, MAOIs, and TCAs
    - Side effects and toxicity became apparent

History of TCA Development

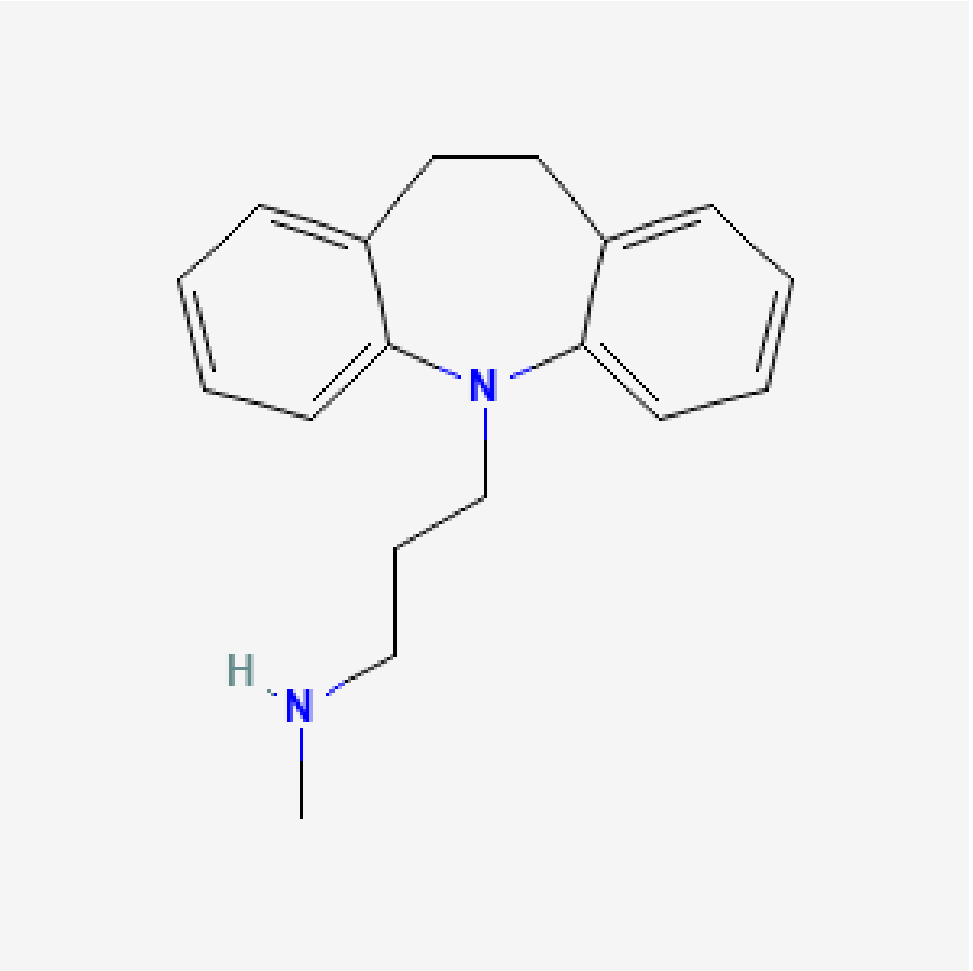
- "Pharmacologic Bridge" paradigm
  - Great heuristic value
  - Limitations
  - Encouraged "me too" drug development
- TCAs provided scientific insights and clinical (and financial) incentives for developing the next generation of antidepressant medications
  - Elucidated the biology of neurotransmission (including the dynamic nature)
  - "Medicalized" depression
  - Emphasized biogenic amines

TCA Structure: 3º vs 2º Amines

Imipramine



Desmethyl-imipramine (Desipramine)



Pharmacodynamics

- 3^{o} amines (in general):
  - Block 5-HT reuptake
  - Are metabolized (demethylated) to 2^{o} amines
  - Relatively potent H_1 blockade
  - Relatively potent ACH blockade
  - Relatively potent alpha-adrenergic blockade

Pharmacodynamics

- 2^{o} amines (in general):
  - Block NE reuptake
  - *Relatively less* potent H_1 blockade
  - *Relatively less potent* ACH blockade
  - *Relatively less potent* alpha-adrenergic blockade

A Plethora of Options

- 8 (plus 1)TCAs
  - 3º amines: imipramine; amitriptyline; trimipramine; clomipramine*
  - 2º amines: desipramine; nortriptyline; doxepine; protriptyline
  - misc: amoxapine (structurally similar to loxapine; NE reuptake inhibitor and post-synaptic DA receptor antagonist)
- 1 tetracyclic: maprotiline (side chain identical to desipramine, nortriptyline, and protriptyline)

* not “officially” an antidepressant

Pharmacokinetics

- Most TCAs are quickly and nearly completely absorbed (typical peak blood level within 2-8 hours)
- Reasonably long half-lives
  - Once/day dosing OK
  - In overdose, linear clearance is not always maintained
- Plasma concentration/response
  - Nortriptyline has an inverted U dose/response relationship
  - Blood level/response relationships for DMI, IMI, for inpatients

Side Effects/Toxicity

- Prior vulnerability (pre-existing conduction problems, orthostatic hypotension, seizure disorder) increases risk
- CNS
  - Confusion/delirium
  - Drowsiness/fatigue
- Anticholinergic
  - dry mouth; constipation, blurred vision, urinary retention
  - 3^{o} amines > 2^{o} amines (AMI worst; DMI least)

Side Effects

- Antihistaminic
  - Doxepin is a more potent H_1 antagonist than diphenhydramine
  - Sedation/drowsiness
- Other/Misc
  - Weight gain (3^o amines > 2^o amines)
  - Sexual dysfunction appears to be < SSRIs (? Reporting artifact)

Overdose

- Narrow therapeutic window:
  - 10-day supply is approximate LD_{50}
- Most common cause of death: cardiac arrhythmia
  - Seizures
  - CNS depression
  - Respiratory depression
- Total AMI OD deaths reported in poison control centers from 2000 – 2014 was > than the total for all other tricyclic and tetracyclics and > than all second-generation antidepressants combined (Nelson and Spiker 2017)

Indications/Efficacy

- Major Depressive Disorder
  - Imipramine (most studied) 65% response rate vs. 30% placebo
  - Maintenance (3 years): 80% (full dose IMI) vs. 10% placebo
  - MDD with Melancholic Features: similar efficacy to SSRIs
  - MDD with Atypical Features: IMI efficacy > placebo but < MAOIs
  - MDD with Psychotic Features: less effective than combination with antipsychotic

Indications/Efficacy

- Major Depressive Episodes
  - MDE in Bipolar Disorder: increased risk of “switch” to mania or induction of rapid cycling as monotherapy
  - Persistent Depressive Disorder: TCAs outperform placebo; comparable to sertraline
  - Depressive Disorders in Children: no better than placebo
  - MDD in Older Adults: Limited data. One controlled study of NOR in 80+ year olds in a residential care facility found superiority over placebo

Other Indications

- Panic Disorder: Superior to placebo. Start at low dose
- OCD: CMI is well established, superior to 2^{o} amine TCAs
- AD/HD: DMI is superior to placebo, although stimulants remain first line treatment. (DMI has low abuse potential, but cardiac effects in children are a concern)
- Pain Syndromes: Bigger effect size in treating various pain syndromes than in treating depression. Dosing requirements are lower and onset of action quicker c/w treating depression.
- Nocturnal Enuresis: Low dose IMI is effective in children

A Simple Approach:

- Become familiar with 2 of the TCAs:
  - A 3º amine (e.g., imipramine)
  - A 2º amine (e.g., desipramine)
  - (can also consider clomipramine for OCD)

A Simple Approach:

- I.M.O.:

  No oral antidepressant treatment has superior efficacy in treating depression than the others

  (caveat: a few, e.g. trazodone, may be inferior)

  Therefore, select a treatment based on side effect and safety profile for each individual patient

  In this regard, TCA will not often be the first line choice

A Really Bad Candidate for TCA Treatment:

- Elderly man with:
  - Bipolar Depression
  - Psychotic Features
  - H/O multiple suicide attempts
  - Lives alone
  - No active therapeutic relationship
  - History of poor adherence to treatment, including “self-medicating”

A Really Bad Candidate for TCA Treatment:

- Additional medical/social features:
  - BPH
  - H/O seizure disorder
  - Cardiac arrhythmias
  - Recent history of falls when getting out of bed or standing up
  - Daughter is a personal injury attorney specializing in medical malpractice

Potentially Good Candidate for TCA Treatment:

- Young, healthy adult:
  - Strong family history of Major Depression
  - No history or family history of bipolar symptoms
  - Both parents and their identical twin responded well to TCA
  - Has strong therapeutic alliance with their psychotherapist
  - Lives with spouse
  - No history of suicide attempt, no suicidal ideation
  - Very concerned about sexual side effects that a friend experienced on SSRIs
  - Mentions chronic allergic rhinitis is bothering them

Potentially Good Candidates for TCA Treatment:

- If the patient presents with agitation, insomnia, loss of appetite, weight loss
  - Consider a sedating TCA at bedtime (e.g., IMI)

Potentially Good Candidates for TCA Treatment:

- If the patient presents with fatigue, hypersomnia, decreased energy and concentration
  - and has a seizure disorder (not a candidate for bupropion)
  - and is phobic about venipuncture (not a candidate for NOR)
  - consider an activating, noradrenergic TCA (e.g., DMI)

General Principles for TCA Treatment:

- Start low…
- Go slow… (remember it takes 5 half-lives to reach steady state)
- Educate patient on timeline, including need for continuation phase of treatment
- Give limited supply and check for compliance (e.g., should see some side effects)

A Variation on Shannon’s Girl Scout Song:

- “Make new friends but keep the old…
  One is silver and the other gold…”
- “Embrace new treatments but remember the old…
  One, the ‘new guy’, may be oversold…”

Questions? Thank you!