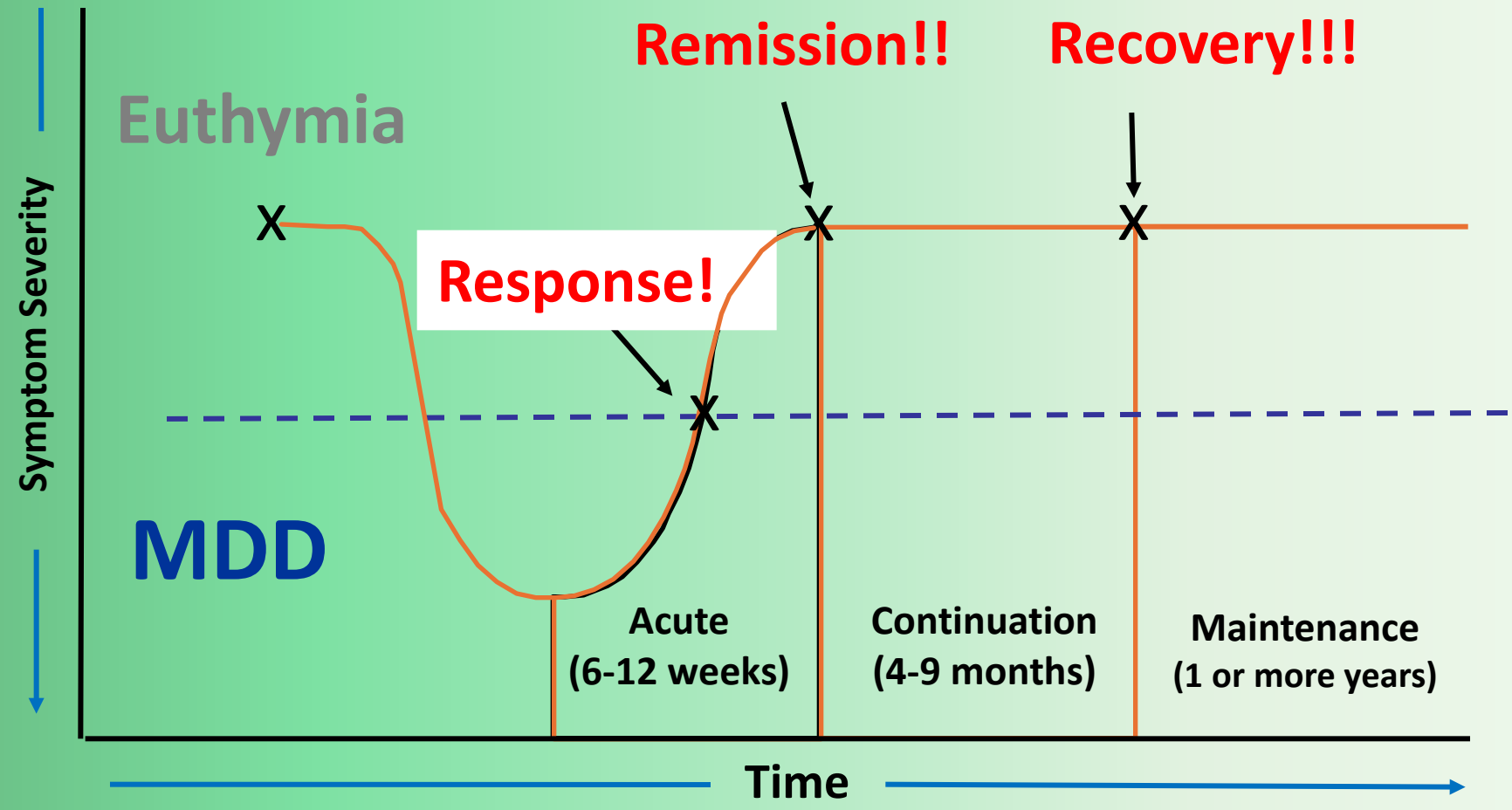
BRIDGES TO MENTAL HEALTH

Advanced Pharmacology for Depression

Treatment of Major Depressive Disorder (MDD): The Idealized Version

BRIDGES TO MENTAL HEALTH



Adapted from Kupfer DJ. *J Clin Psychiatry* 1991;52 (Suppl):28–34.

The reality in between…

BRIDGES TO MENTAL HEALTH

- Antidepressants (and other depression treatments) are often highly effective and sometimes life saving; however...
- Only ~ 1 in 2 depressed individuals respond to a first course of antidepressants
- Only ~ 1 in 3 depressed individuals achieve full remission of symptoms on a first course of antidepressants

The reality…

BRIDGES TO MENTAL HEALTH

- Response to treatment is often delayed by weeks (or months)
- Over 4 in 10 individuals who respond or remit experience a relapse of depression over the course of the next year requiring further treatment
- For many individuals, it takes multiple attempts at treatment to reach a stable recovery

Distinguishing between Treatment Resistance and Treatment Intolerance

BRIDGES TO MENTAL HEALTH

- *Intolerance* = difficulty achieving adequate doses and duration of treatments, usually due to side-effects (e.g., dizziness, drowsiness, dizziness, nausea, jitteriness)
- An individual may be *intolerant* of some medications (thereby not able to benefit from a full course) and *resistant* to other medications (tolerating but not responding to a full course)

Clinical Approach to Treatment Resistant Depression: Re-checking the basics

BRIDGES TO MENTAL HEALTH

- ✓**Adherence:** ambivalence, stigma, cognitive problems, cost
- ✓**Diagnosis:** e.g., bipolar disorder, personality disorder, dementia, psychosis, brain lesion
- ✓**Comorbidity:** Substance use, OCD, PTSD, other medical conditions (e.g., hypothyroidism)
- ✓**Pharmacokinetics:**
  - Poor absorption
  - Rapid metabolizer
  - Drug-drug interactions

Major Pharmacological Approaches for Treatment Resistant Depression

BRIDGES TO MENTAL HEALTH

- ✓ Dose Increase
- ✓ Switching
- ✓ Augmentation
- ✓ Combination

Ionescu D, Rosenbaum JF, Alpert JE *Dialogues in Clinical Neuroscience* 2015; 17:111-126.

Dose Increase

BRIDGES TO MENTAL HEALTH

- Definition:
  - The use of doses higher than those considered standard for a given antidepressant
- Rationale:
  - To increase the chance of obtaining adequate blood levels in rapid metabolizers
  - To obtain a different neurochemical effect (e.g., going from a relatively selective serotonergic effect at lower doses to a dual-action effect at higher doses)

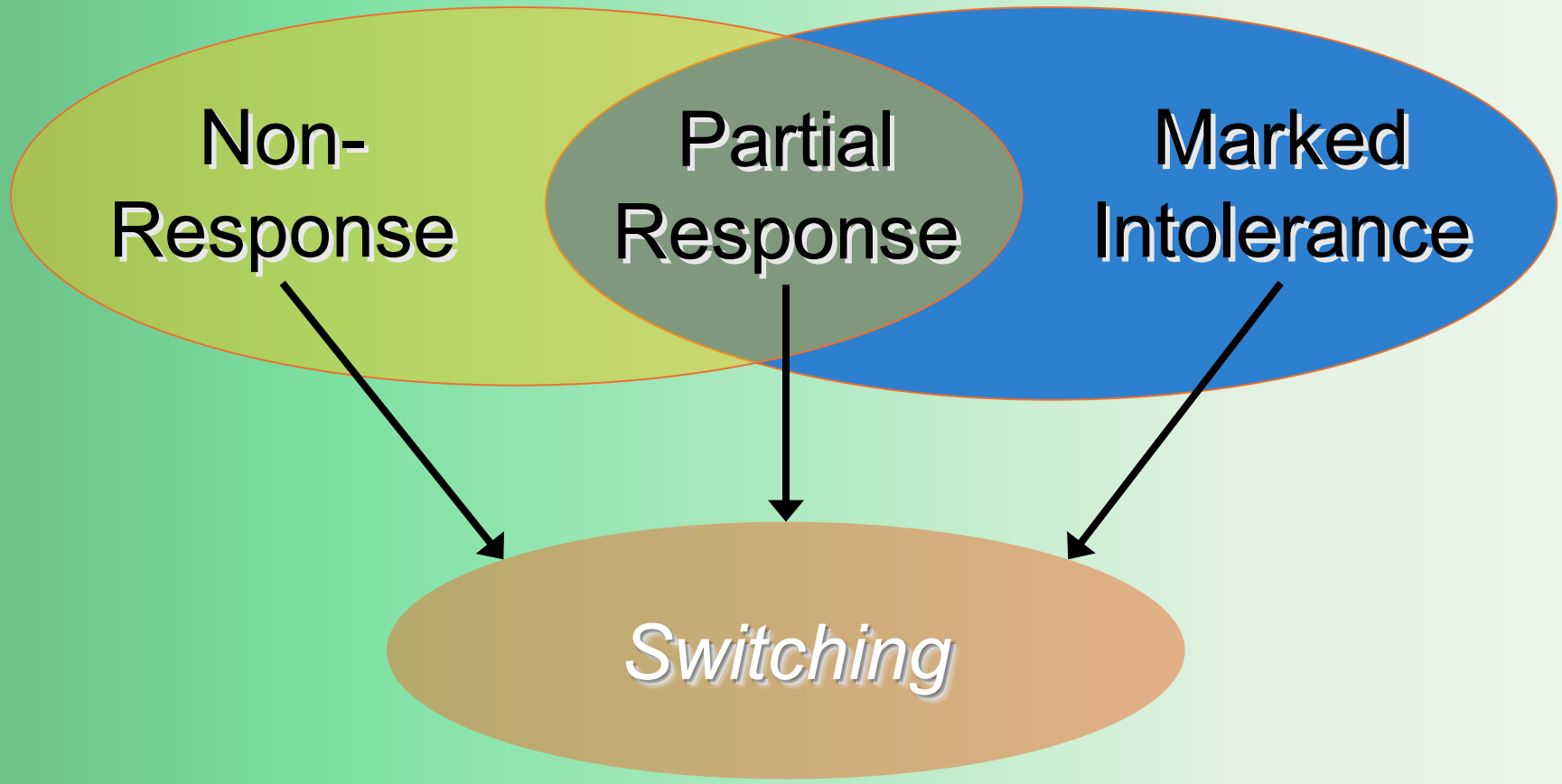
Dose Increase: Practical Issues

BRIDGES TO MENTAL HEALTH

- Gradual increasing the dose by 50-100%
- Wait at least 4 weeks before deciding whether this strategy helps
- If no side effects are present, consider increasing the dose further
- Blood levels may be informative (even with SSRIs or other newer antidepressants)

Switching

BRIDGES TO MENTAL HEALTH



Switching: Rationale

BRIDGES TO MENTAL HEALTH

- Switch within Class:
  - There may be some differences across agents within the same class in pharmacological properties in vitro or in vivo (e.g., relatively greater uptake inhibition of other neurotransmitters such as norepinephrine or dopamine)
- Switch to a Different Class:
  - To obtain a different neurochemical effect (e.g., from a relatively serotonergic agent to a relatively noradrenergic agent)
  - A specific depressive subtype may be more responsive to one antidepressant class than another

Switching

BRIDGES TO MENTAL HEALTH

Switching within class (e.g., SSRI to SSRI) is generally as successful as switching between classes (e.g., SSRI to SNRI) -- with the following exceptions:

- **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and TCAs** may be superior to Serotonin Reuptake Inhibitors (SSRIs) in MDD with **comorbid pain** (e.g., fibromyalgia, diabetic neuropathy)
- **Bupropion** may be superior to SSRIs and SNRIs for MDD with antidepressant related **sexual dysfunction, nicotine dependence, or Attention Deficit Hyperactivity Disorder** (ADHD)
- **Monomaine Oxidase Inhibitors (MAOIs)** are superior to Tricyclic Antidepressants (TCAs) in MDD with **atypical MDD features** (oversleeping, carbohydrate craving, rejection sensitivity and mood reactivity)
- **More complex agents** (e.g., SNRIs, TCAs) may be superior to simpler agents (e.g., SSRIs) for **more severely ill populations**

Switching: Practical Approaches

BRIDGES TO MENTAL HEALTH

- Gradual tapering the first agent while starting the new one
  - Side effects of the new drug may be intensified by the concurrent presence of the first agent
  - "Start low and go slow" with the new agent
  - Consider possible drug-drug interactions
- Abrupt replacement with within class-switches
- Wash-outs are necessary with MAOIs [either when you start them (2-5 weeks) or when you stop them (2 weeks)]

Switching: TCAs

BRIDGES TO MENTAL HEALTH

- Historically most used; 60%-80% response reported in open studies
- Adverse effects- anticholinergic, cardiac
- Sudden death? Can be lethal in overdose

Switching: TCAs

BRIDGES TO MENTAL HEALTH

- Increased response
  - Inpatients with severe melancholic depression*
  - Psychotic depression** (patient should also should be on antipsychotic)
  - Post-psychotic depression in schizophrenia

*Nobler MS, Roose SP. Differential response to antidepressants in melancholic and severe depression. Psychiatric Annals. 1998;28:84-88

**Spikar DG et al. Am J Psychiatry 1985;142:430-436

Switching: TCAs (e.g. nortriptyline)

BRIDGES TO MENTAL HEALTH

- Caution: Overdose risk. 10 day supply can be fatal
- Contraindicated if recent MI, ischemic heart disease, cardiac conduction defects, urinary retention, untreated glaucoma, renal failure, orthostasis (but nortriptyline has least)
- Obtain baseline EKG. If bundle branch block, risk of serious arrhythmia is higher. Check at least one blood level to rule out slow metabolism and risk of fatal cardiac toxicity. (Preskorn, 1994)
- Begin nortriptyline 5 mg tid. Increase by 5 mg every two days until you get to 50 mg and then increase by 10 mg every two days until you get to 100 – 150 mg given in one dose. If response unsatisfactory after 4 weeks and results have plateaued get a blood level.

Switching: TCAs (e.g. nortriptyline)

BRIDGES TO MENTAL HEALTH

- Side Effects Related to Receptors that are Hit
  - Norepinephrine: tremors, tachycardia, sexual dysfunction, postural hypotension (least with nortriptyline), reflex tachycardia
  - Serotonin: GI disturbance, anxiety, sexual dysfunction
  - Dopamine: EPS and prolactin increase (amoxapine)
  - Histamine: drowsiness, weight gain (amitriptyline, clomipramine)
  - Acetylcholine: Blurred vision, dry mouth, constipation, urinary retention, impaired memory (least with desipramine, most with amitriptyline)

Switching: MAOIs

BRIDGES TO MENTAL HEALTH

- Phenelzine (Nardil)
- Tranylcypromine (Parnate)
- Isocarboxazid (Marplan)

Switching: MAOIs

BRIDGES TO MENTAL HEALTH

- Indications: **Atypical Depression** (if SSRIs fail)
- DSM Criteria: 2 out of 4 of…
  - Hypersomnia
  - Appetite Increase
  - Leaden paralysis (heavy sensation in limbs)
  - Rejection sensitivity
- Indication: Refractory Depression
- Indication: Social Anxiety Disorder and other refractory anxiety disorders

Switching: MAOI Dosing

BRIDGES TO MENTAL HEALTH

- Begin MAOI diet several days before starting
- Discontinue fluoxetine x 5 weeks; others 2 wk

- Most common reason for discontinuation?
  - Orthostatic hypotension

Switching: MAOI Liver Issues

BRIDGES TO MENTAL HEALTH

- Phenelzine and isocarboxazid are hydrazide-related MAOIs and as such carry a small but significant risk of hepatocellular injury. Avoid in patients with liver disease.

Switching: MAOI Dietary/ Medication Interactions

BRIDGES TO MENTAL HEALTH

- Foods to Avoid
  - Aged cheeses
  - Yeast extract
  - Red wine, beer, ale
  - Overripe, fermented or pickled foods
  - Fava beans
  - Ginseng
  - Caffeine*
  - Soy sauce*
- Medications to Avoid:
  - Many antidepressants
  - Meperidine
  - Stimulants*
  - Decongestants
  - L-DOPA*
  - Propranolol*
  - Dextromethorphan
  - Some anesthetics*
  - If uncertain, ask!

**May be safe in limited amounts and/or with appropriate monitoring*

Augmentation

BRIDGES TO MENTAL HEALTH

- **Adding a non-antidepressant to an antidepressant**
- Typically in setting of partial response to first agent
- Opportunity to broaden pharmacological profile well as to target side-effects (e.g., sedation)
  - **Atypical antipsychotics** (olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone)
  - **Dopamine agonists** (pramipexole) and **psychostimulants** (methylphenidate, dextroamphetamine, modafinil)
  - **Lithium**
  - **Thyroid** (T3; triiodothyronine)
  - **Buspirone**
  - **Pindolol** (may accelerate response rather than increase response)
  - **Naturally occurring agents:** L-methylfolate, S-Adenosyl Methionine (SAMe), creatine, omega-3 fatty acids, cycloserine

Augmentation

BRIDGES TO MENTAL HEALTH

- Definition: the use of a psychotropic agent (without per se an indication for depression) to enhance the effect of an antidepressant
- Rationale:
  - To obtain a different neurochemical effect by adding an agent affecting different neurotransmitter systems
  - To broaden the therapeutic effect (e.g., by adding an anti-anxiety agent to an antidepressant)
  - To combine agents with different mechanisms of action and/or indications

Lithium Augmentation

BRIDGES TO MENTAL HEALTH

- Lithium augmentation (> 600 mg/day) of TCAs, MAOIs, and SSRIs (Bauer M, Dopfmer S. J Clin Psychopharmacol. 1999 Oct;19(5):427-34.)
- Disadvantages:
  - Relatively low response rates in most recent studies (Fava M et al. J Clin Psychopharmacol. 2002 Aug;22(4):379-87; Nierenberg AA et al. J Clin Psychopharmacol. 2003 Feb;23(1):92-5)
  - Risk of toxicity (Salama AA, Shafey M. Am J Psychiatry. 1989 Feb;146(2):278.)
  - Need for blood monitoring
- Advantage: The pooled odds ratio (from 9 studies) of response during lithium augmentation compared with placebo is 3.31 (95% confidence interval: 1.46-7.53) (Bauer M, Dopfmer S. J Clin Psychopharmacol. 1999 Oct;19(5):427-34.)

Thyroid Augmentation

BRIDGES TO MENTAL HEALTH

- Thyroid hormone augmentation (25-50 mcg/day) (Aronson R et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.)
- L-triiodothyronine (T3) has been used in preference and has been thought to be superior to thyroxine (T4) (Joffe RT, Singer W. Psychiatry Res. 1990 Jun;32(3):241-51.)
- Disadvantages:
  - All published controlled studies concern TCAs (Aronson R et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.) and only uncontrolled studies pertain to SSRIs (Agid O. Int J Neuropsychopharmacol. 2003 Mar;6(1):41-49; Iosifescu D et al. J Clin Psychiatry. 2005 Aug;66(8):1038-42)

Combination

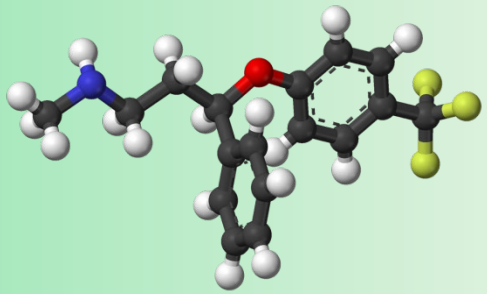
BRIDGES TO MENTAL HEALTH

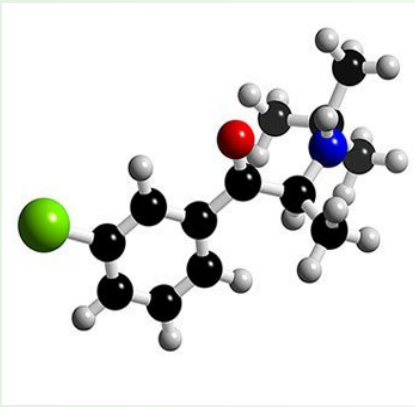
- Definition: The concomitant use of two antidepressants to enhance their therapeutic effect
- Rationale:
  - To obtain a different neurochemical effect by combining antidepressants affecting different neurotransmitter systems
  - To combine antidepressants with different mechanisms of action

Combination

BRIDGES TO MENTAL HEALTH

- **Antidepressant + Antidepressant**
- Similar context as augmentation: partial response
- Examples of Antidepressant Pairs
- SSRI or SNRI *plus* Bupropion
- SNRI *plus* Mirtazapine





Conclusions

BRIDGES TO MENTAL HEALTH

- Treatment resistance is common in MDD
- Many strategies may be effective approaches for partial and non-responders to antidepressant treatment
- The potential loss of partial benefit from the failed trial may reduce the feasibility of switching strategies
- The presence of significant side effects from the antidepressant itself may reduce the acceptability of dose increase, switching, augmentation and combination strategies