Psychotropic Drug Interactions

- Over the past 2 decades:
  - Treatment options: Several drug and non-drug therapies
  - Increasing number of psychotropic drugs
  - Increased risk of adverse outcomes
- Overwhelming information on drug-drug interactions
- Over 50% of ADRs among hospitalized patients - attributed to drug-drug interactions
- This workshop: A refresher on psychiatric drug interactions
- Aim: Optimize patient safety.

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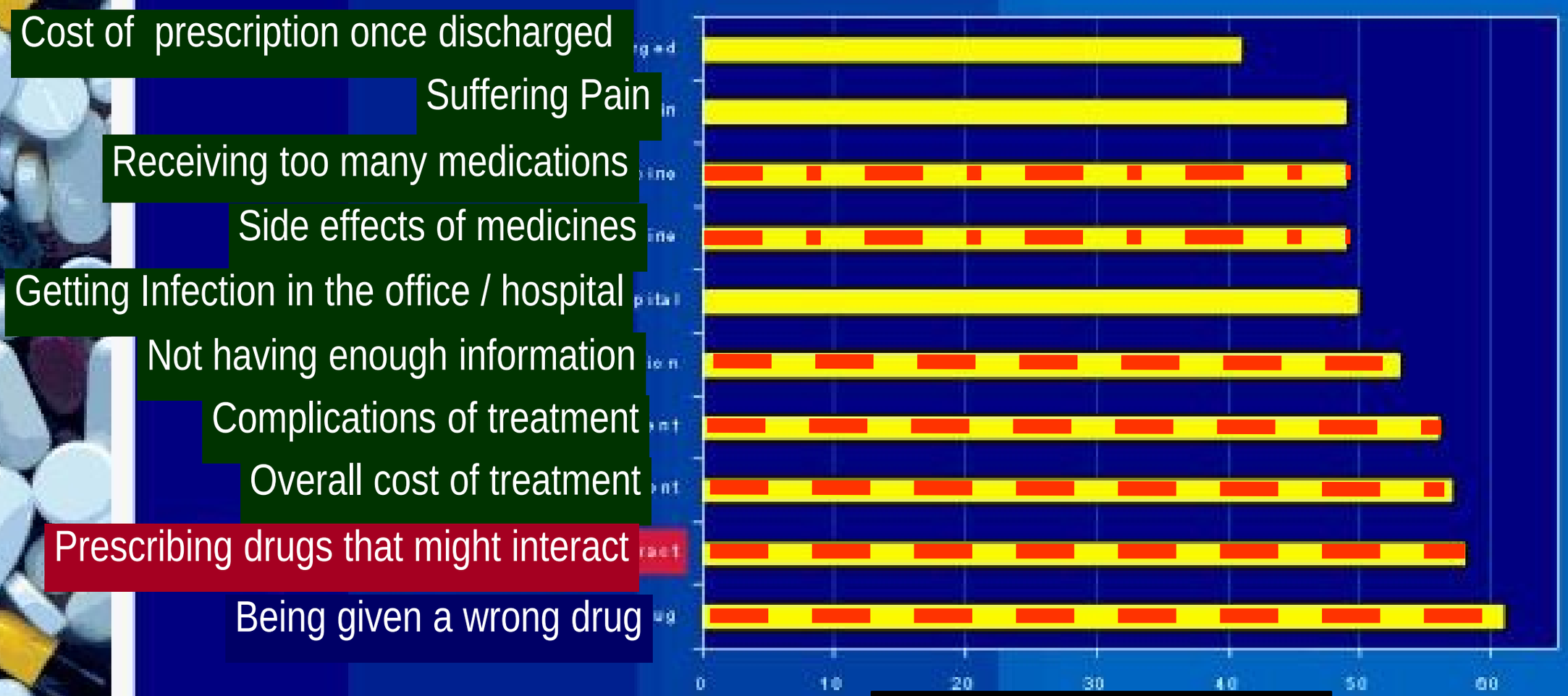
Tommie LD. 2012. Psychotropic Drug-Drug interactions, A Refresher. US Pharmacist. 37(11) HS-16-HS-19
Downloaded from: http://www.medscape.com/viewarticle/775394 18.06.2015 - Adapted

Centers for Education & Research on Therapeutics™

Primary Worries in Primary Care: 1008 Patients



Source: American Society of Health Systems Pharmacists. ASHP Patient Concerns National Survey Research Report, 1999.

Psychotropic Drug Interactions

- Basics:
  - Prescriptions ought to reflect current state of 'evidence'
  - Evidence based prescriptions are effective and safe
  - Each prescriber and user: Personal preference of drugs and drug combination
  - This workshop is to facilitate / revise prescribing practices

✓ All ingested drugs and substances (*SUBSTRATE*) are metabolized primarily by the liver, sometimes in the GI tract.

- Drug and substance metabolism is aimed at detoxifying and eliminate every exogenous and endogenous substrate.
- Applied inhaled or injected substances may or may not be metabolized by the liver (first pass metabolism)
- Prodrug: A precursor chemical compound of a drug administered to improve bioavailability:
  - Improve absorption from the gastrointestinal tract.
  - Improve how selective receptor action
  - Reduce adverse or unintended effects of a drug, - ADRs

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Drug therapy

» Monotherapy or one-drug therapy

» Polypharmacy:

» Perspectives:

- Synergistic actions,
- Adjuvant actions,
- Antagonist actions,
- Cumulative effects,
- Prophylaxis,
- Idiosyncratic drug effects and interactions
- ……

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Drug-Drug Interactions You Need to Know

The Carlat Psychiatry Report

✓ Drug interactions are enormously complicated.

★ Carlat report is an attempt to simplify *fundamentals* of psychotropic drug prescriptions.

Psychotropic drug-drug interactions: meet two criteria:

a) Psychiatrists commonly encounter them;

b) They are likely to cause clinically significant problems

✓ A quick summary reference:

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1. Aim: To avoid significant *increase* in the levels of another drug:

   ✳ Avoid co-prescribing: Fluoxetine, Paroxetine, high dose Sertraline, Fluoxamine, Nefazodone, Valproate and ask your patient to stop drinking Grapefruit Juice.

2. Aim: To avoid significant *drop* in levels of another drugs:

   ✳ Avoid co-prescribing: Carbamazepine, St. John's Wort and ask your patient to stop smoking.

http://pro.psychcentral.com/drug-drug-interactions-you-need-to-know/001578.html 10.06.15

Psychotropic Drugs: actions and interactions

- ✦ Dopaminergic drugs
- ✦ Serotonergic drugs
- ✦ Cholinergic drugs
- ✦ Glutamatergic drugs
- ✦ Gabaergic drugs
- ✦ Melatonergic drugs
- ✦ Adrenergic drugs
- ✦ Second messenger system modifiers
- ✦ Psychotropic drugs + Drugs for systemic illness
  - ✷ (DM, Cardiac, GI, Malignancy…)

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Adapted: Nassir Ghaemi: Tufts medical center. available at: http://sites.google.com/site/tufutsmooddisorders/education/mood-stabilizers. 08.04.2015

Psychotropic Drugs: actions and interactions

- Clinical consideration while prescribing a drug:
  - Desired effects
  - Undesired effects
  - Side effects
  - Toxic effects
- Dose, frequency of administration, caution, precautions..
- Today’s deliberations: Focussed on Antidepressant Drugs

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Psychotropic Drugs: actions and interactions

Anti Depressant Drugs:

- Options: TCAs / PCAs / SSRI / NSRIs / SRI / NRI / GABA / GM / MT……
- Pharmacodynamics of drug interaction
  - Anticholinergic effects and intoxication
    - Trihexyphenidyl + AAPDs - 'the pines': dry mouth, blurred vision, delirium
    - TCAs + benztopine: constipation, heat stroke, urine retention,
  - Serotonin Syndrome: SSRIs, Opioids, Stimulants, Triptans, St. John's wort…..
  - Sedation,
  - weight gain,
  - cardiac: Torsades de Pointes (TdP)
  - Blood dyscrasia
  - metabolic, reproductive and Androgenic actions,
  - ……
- Pharmacokinetics
  - Absorptions
  - Metabolism
  - Distribution
  - Elimination
  - excretion

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Metabolism - Pharmacokinetics of a drug:

1. Every ingested substance is absorbed from the intestines, metabolized by the liver enzyme.
2. With specific reference to drug metabolism:
   - ✳ Ingested drug is termed 'Substrate', metabolized drug: 'Product'
3. Substrate:
   a. A substance (drug, toxins..) that is metabolized into an end product
   b. Eventually deactivated and eliminated
   c. Rate of absorption & elimination: determines the t_{max} & c_{max} of the drug
4. Prodrug: Initially an inactive agent, metabolized to become an active drug
5. The first-pass effect / Metabolism:
   1. Loss in the quantity of the ingested drug during the process of absorption
   2. Generally related to the liver and gut wall enzymes
   3. Once swallowed the liver metabolizes to a significant extent
   4. Thus the bioavailability of the drug is greatly reduced
6. Determinants:
   1. Factors: enzymes, plasma protein and blood cell binding, and gastrointestinal motility.
   2. Enzymes: GI enzymes in the lumen & the gut wall, bacterial enzymes, & hepatic enzymes

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1 Pond SM, Tozer TN.. First-pass elimination. Basic concepts and clinical consequences. Clin Pharmacokinet. 1984 Jan-Feb;9(1):1-25.
Also available at: (abstract) http://www.ncbi.nlm.nih.gov/pubmed/6362950

Drug metabolism:

» Basics / Fundamental concept / Core Concept[1]

1. Cytochrome: CYP
   a. Major enzyme family, widely referenced in clinical pharmacology
   b. Cause oxidative biotransformation of of most drugs
   c. Named as: Number - letter - number, equivalent of ‘family - genus - species’
2. Uridine 5’- diphosphate glucoronosyl transferases: Ugts:
   a. Activity: Phase II conjugative metabolism that follows phase I oxidative metabolism
   b. Function similar to CYP system also named as 1A4, 2B15….j

3. OATP: .

Organic anion transporting polypeptides: A group of polypeptides that facilitate the absorption of drugs and other substrates.[2,3]

4. P-glycoproteins: Pgp
   a. Line the gut and the blood brain barrier
   b. Control rate of absorption and excretion of the drug / substance: ‘*FIRST PASS EFFECt*’
   c. ‘*extruding*’ transporter: remove substances from the brain and cells back into the blood
   d. P-gp: substrates, inhibitors and inducers. In contrast with OATP, P-glycoprotein (Pgp), also know by several other names, is an efflux transporter: it pushes out drugs and other substances that were absorbed from the intestinal lumen

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1 Sandson N.B. Drug interaction case book. American Psychiatric Publishing. Washington, 2003. 2 Svoboda M et al Organic anion transporting polypeptides (OATPs): regulation of expression and function. Curr Drug Metab. 2011 Feb;12(2): 139-53. Also at : http://www.ncbi.nlm.nih.gov/pubmed/21395542 3 Andrade C. 2015. Personal Communication

Cytochrome Enzymes

- Cytochrome : A set of enzymes that metabolize several endogenous and exogenous substances, including drugs and toxins.
- Perform Phase I metabolism: oxidative metabolism.
- Substrate: The agent that is metabolized by the enzyme
- Product: Metabolic end product – eventual elimination
- Pro-drug: Initially inactive – activated after metabolism

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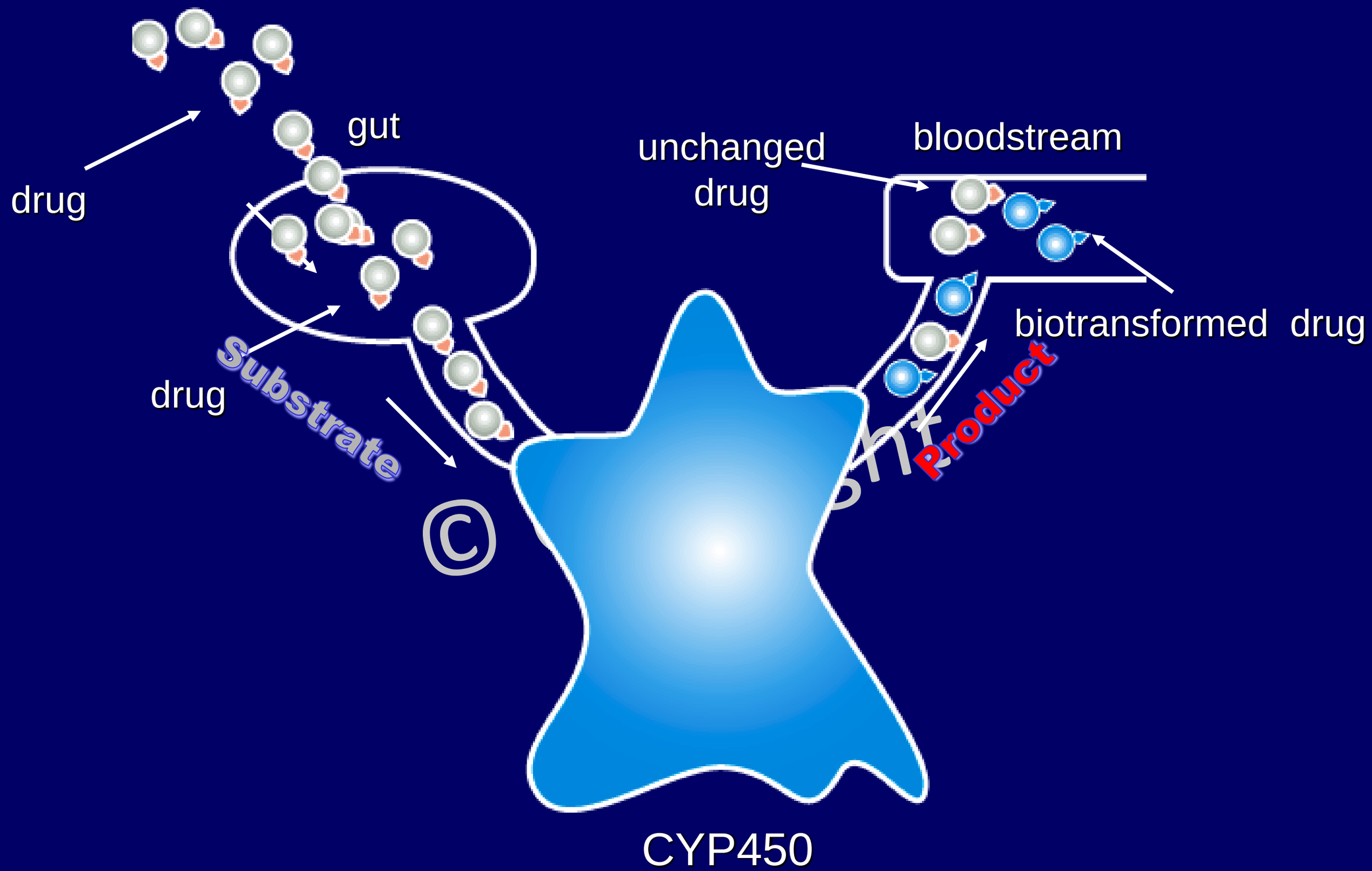

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

Cytochrome Enzymes

Clinical Interventions

1. Inhibition of CYP enzyme actions
   - Competitive
   - Non-competitive / allosteric

2. Induction of CYP enzyme activity

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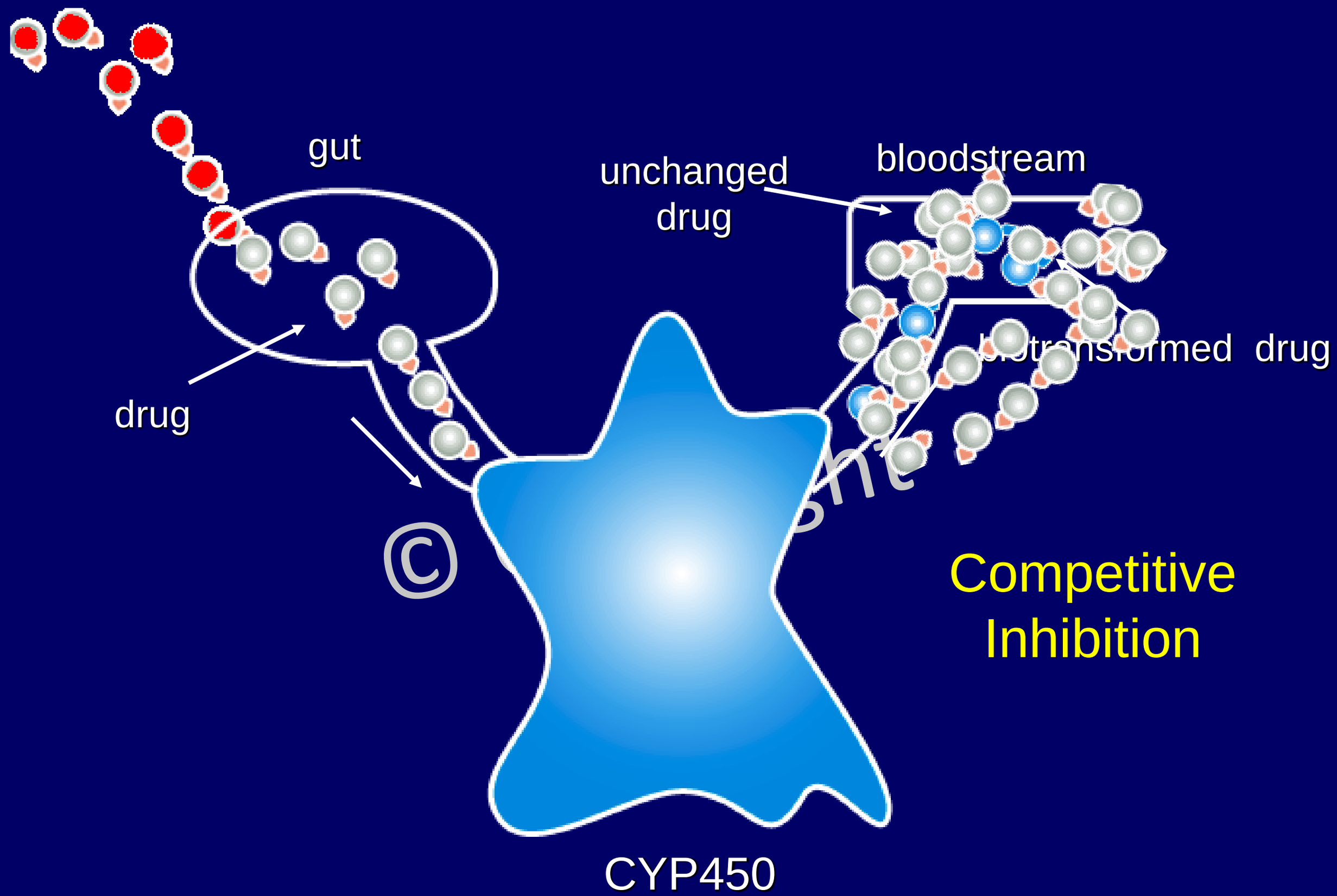
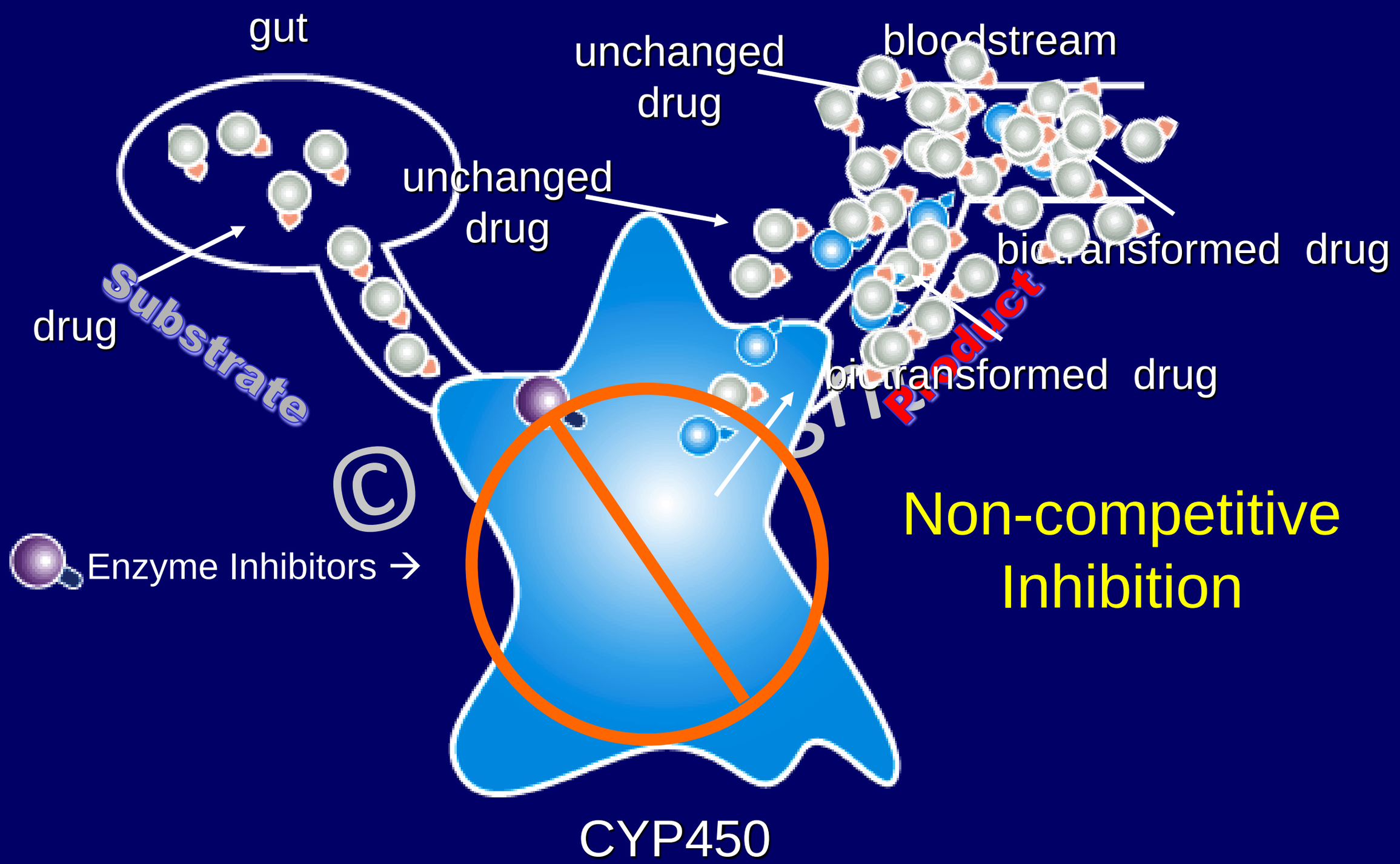


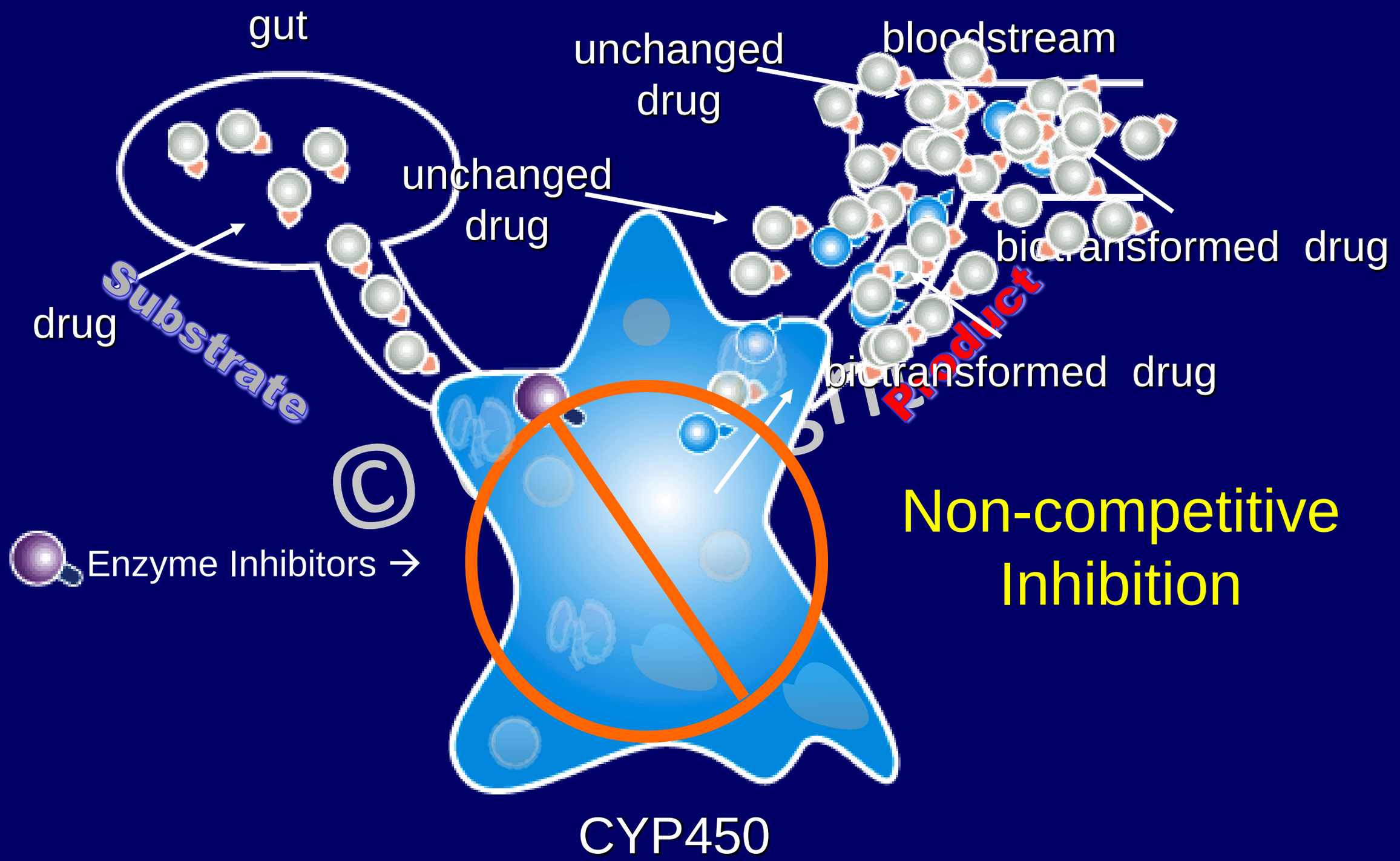
Competitive Inhibition

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



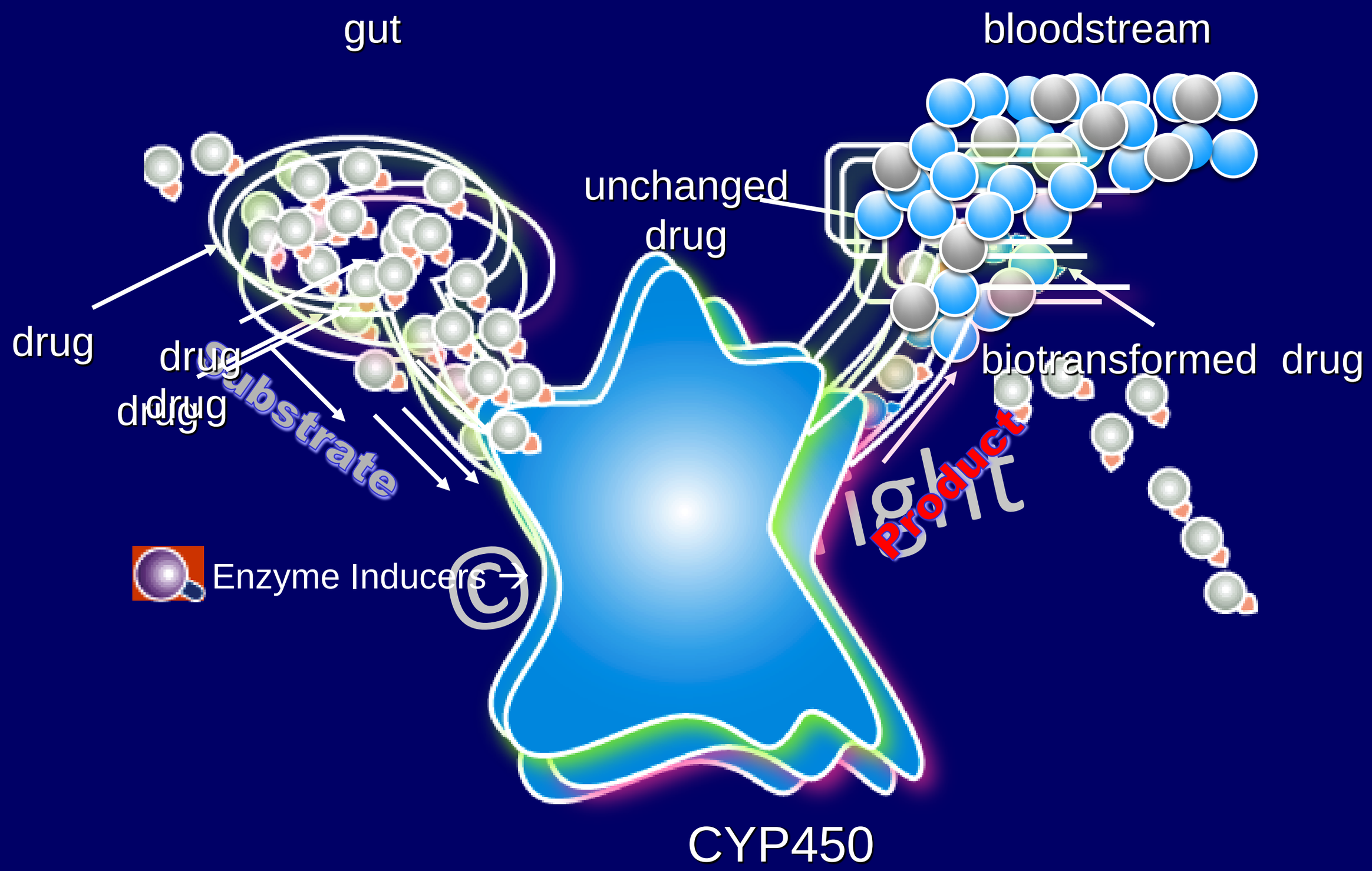
Non-competitive Inhibition

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



Non-competitive Inhibition

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

Drug interactions - CYP

Enzyme inducers	Enzyme inhibitors:
Enhance drug metabolism	Retard drug metabolism
Reduce active drug levels	Elevate active drug levels
Do not affect / alter CYP enzyme activity	Reduce / alter the CYP enzymes activity
Enhance production of the enzymes	Irreversible inhibition of available enzyme

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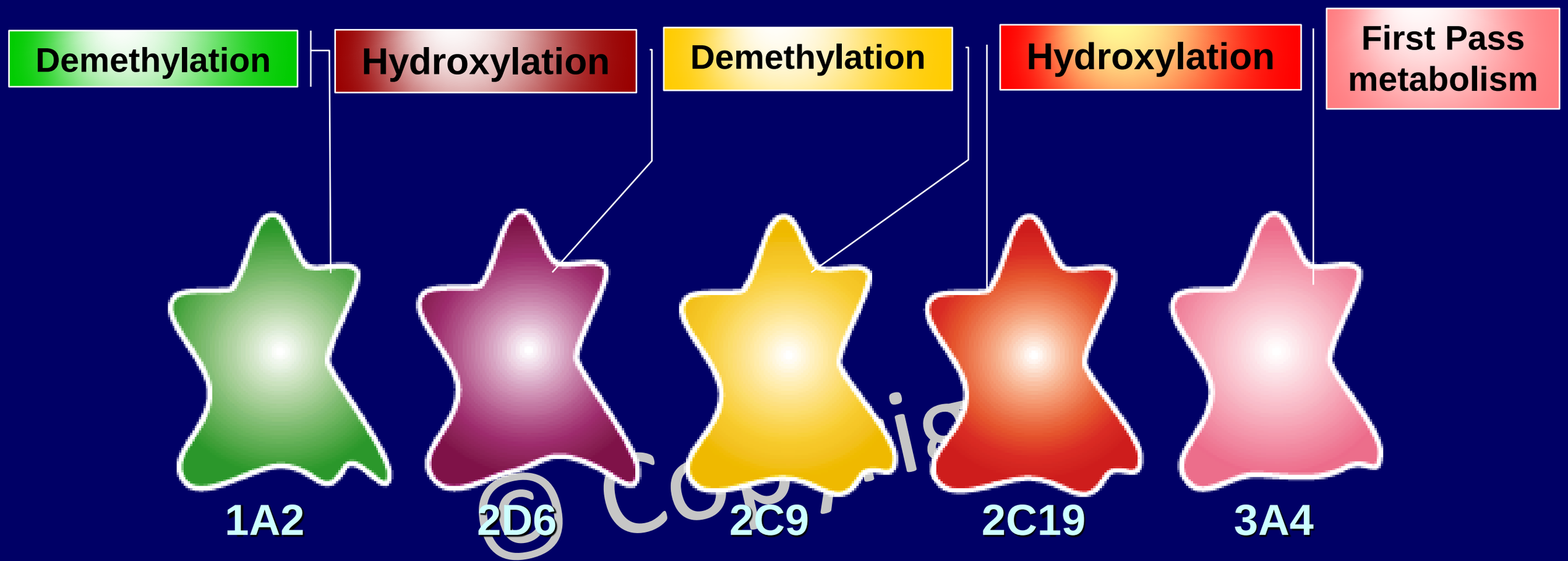

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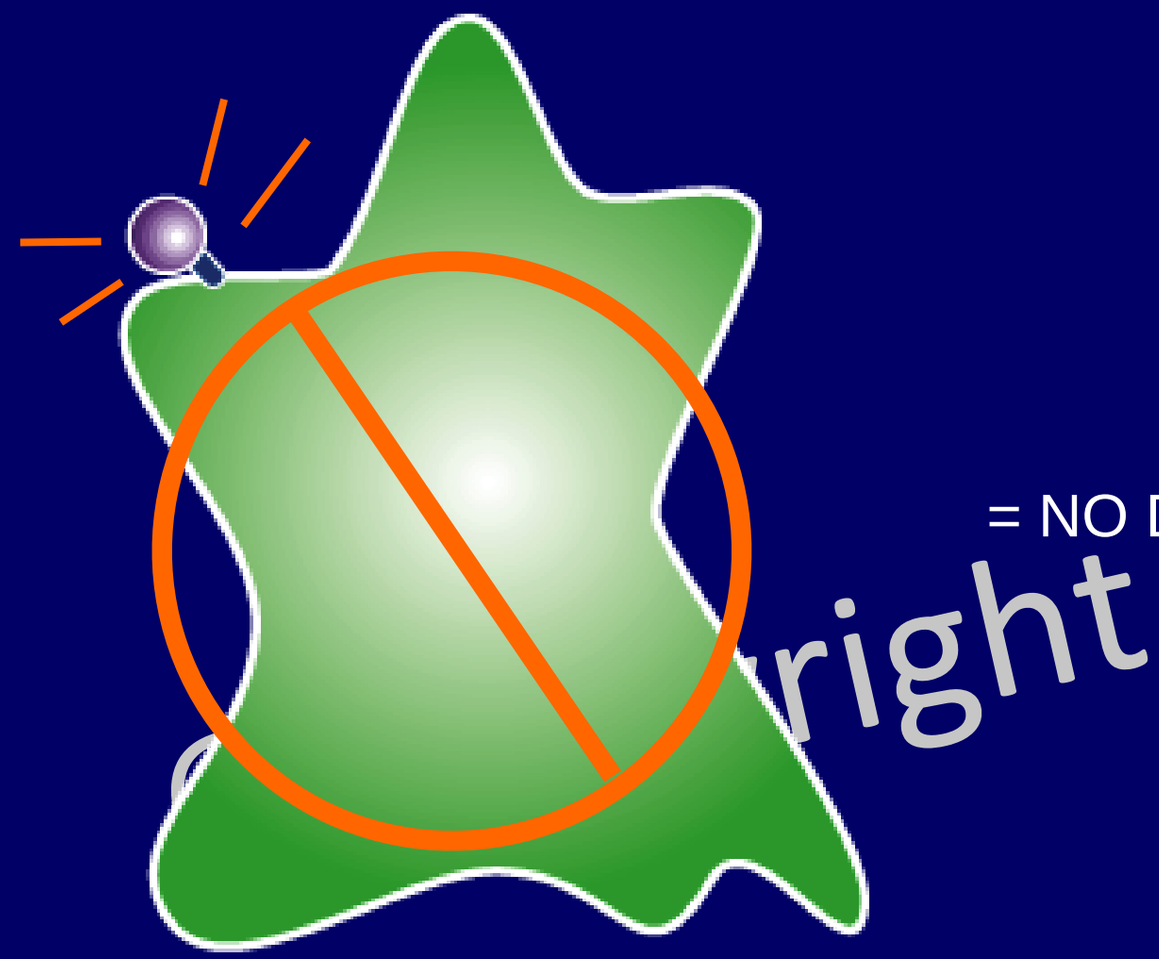
1 = family

A = subtype

1= gene product

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

DEMETHYLATION



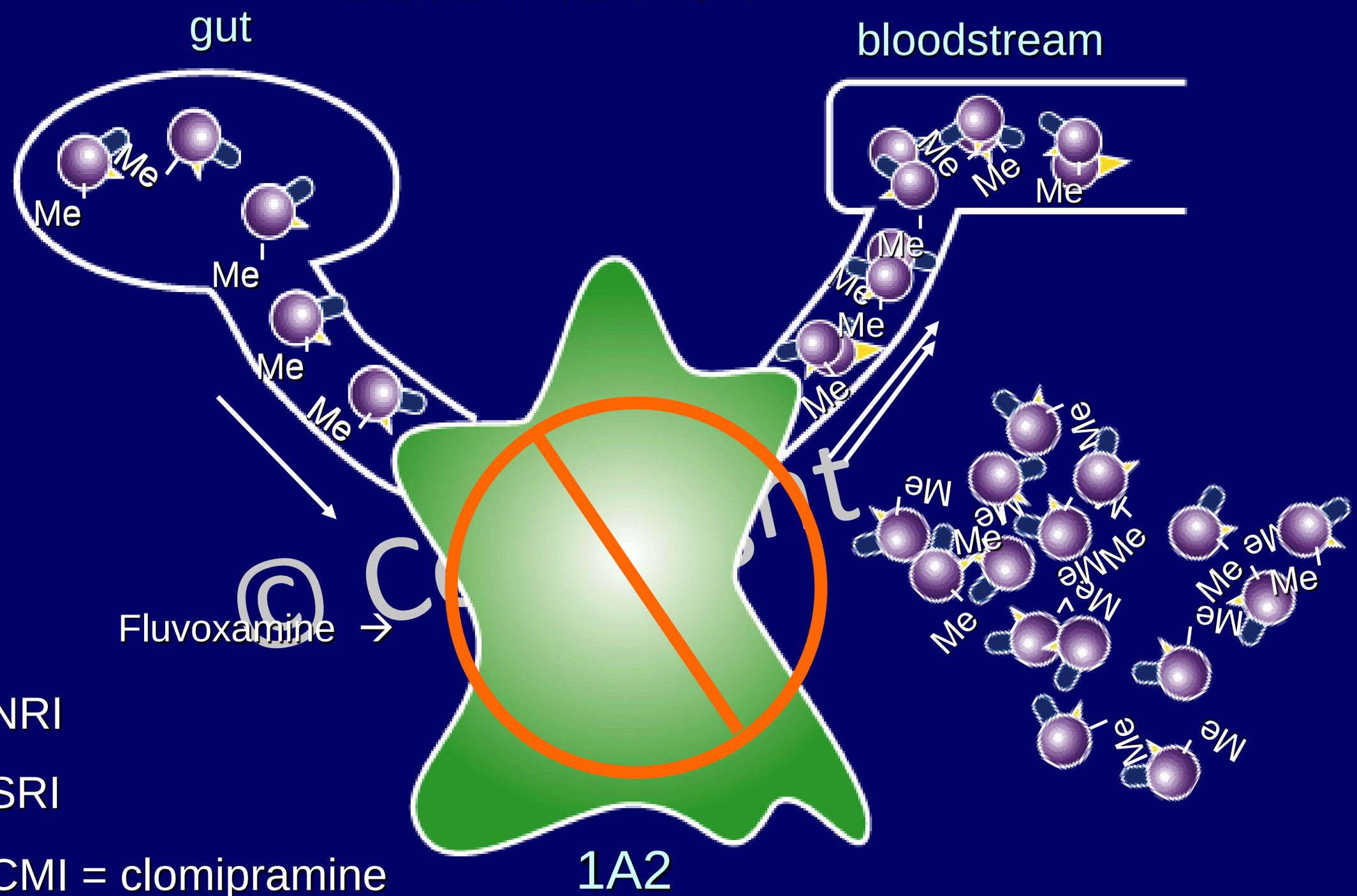
= NO DEMETHYLATION

1A2

= fluvoxamine

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

DEMETHYLATION



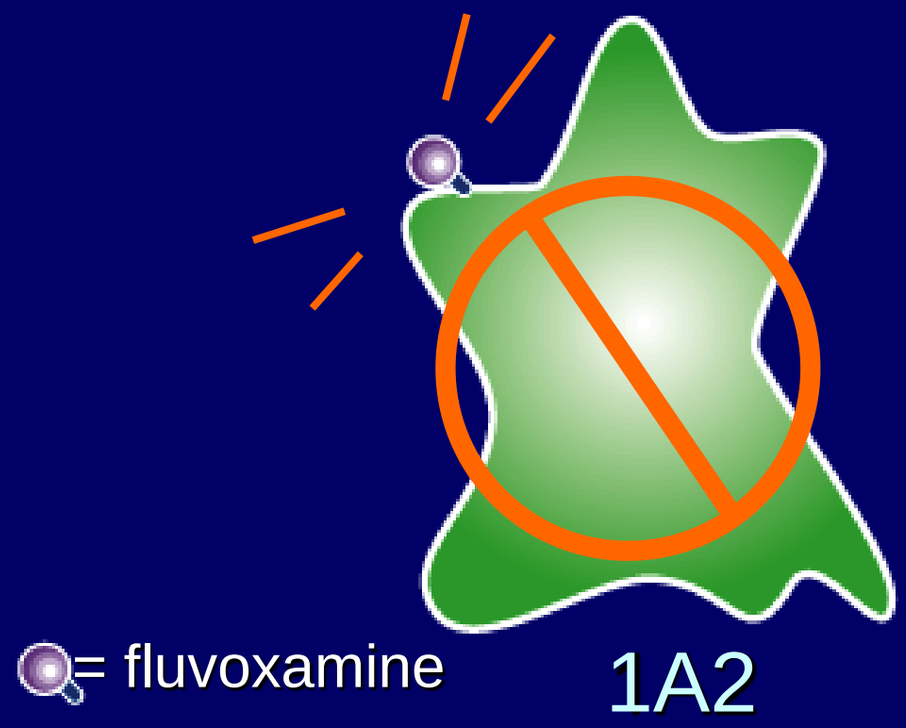
= NRI

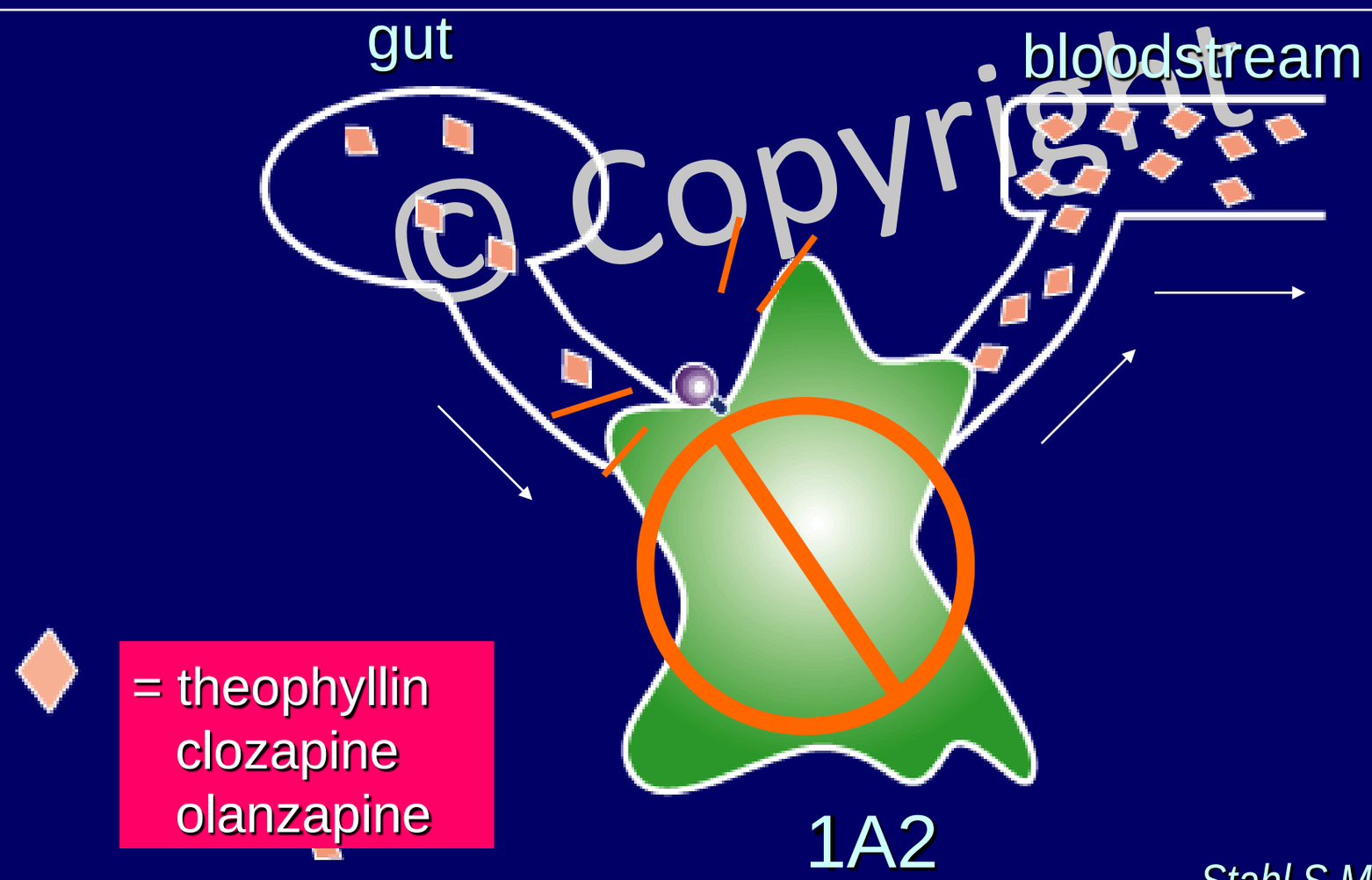
= SRI

= CMI = clomipramine

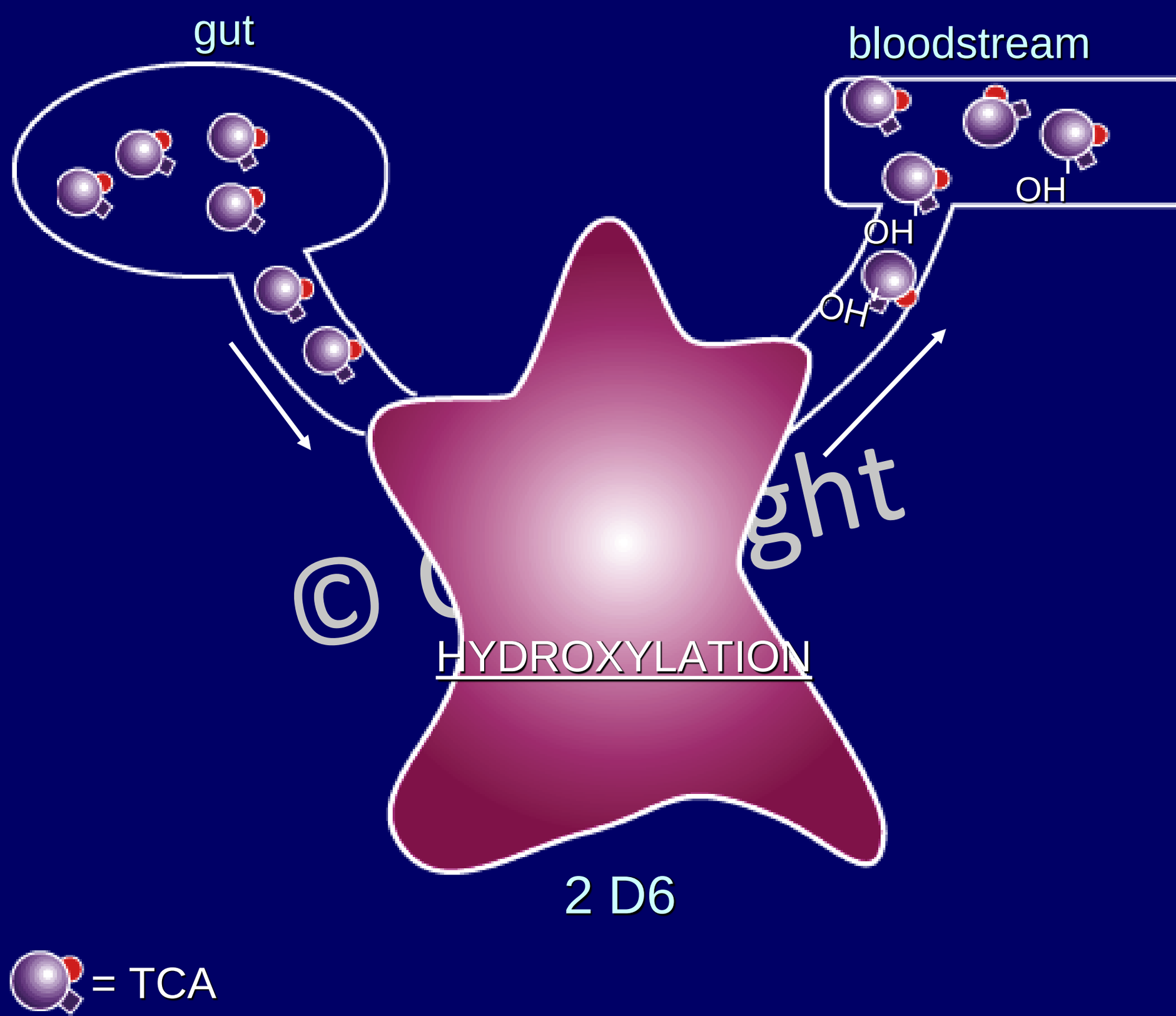
= De-CMI = desmethyl-clomipramine

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000





Stahl S M, Essential Psychopharmacology (2000)



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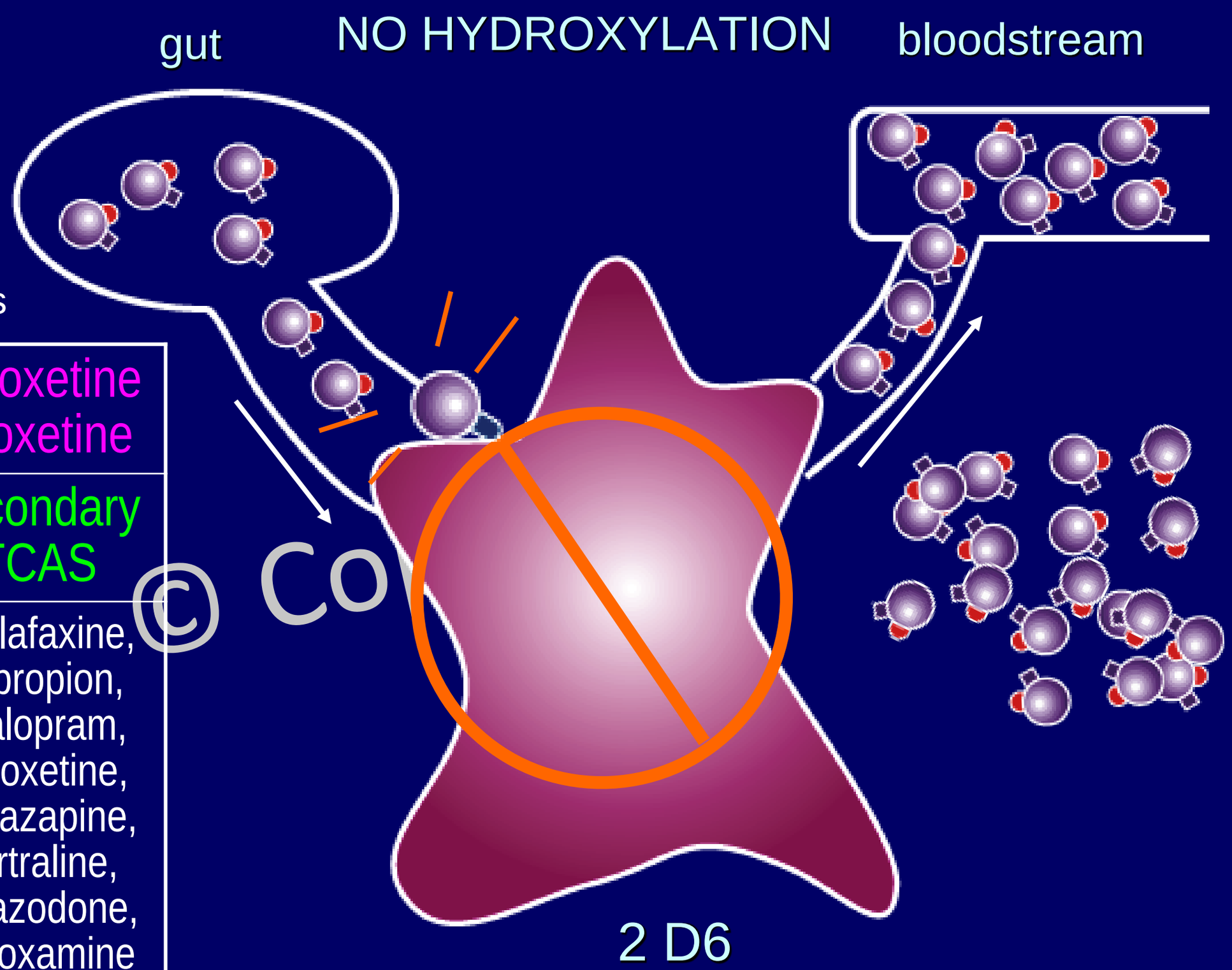

2D6 Inhibitors

High	paroxetine fluoxetine
Moderate to Low	secondary TCAS
Low to Minimal	venlafaxine, bupropion, citalopram, reboxetine, mirtazapine, sertraline, nefazodone, fluvoxamine

= TCA

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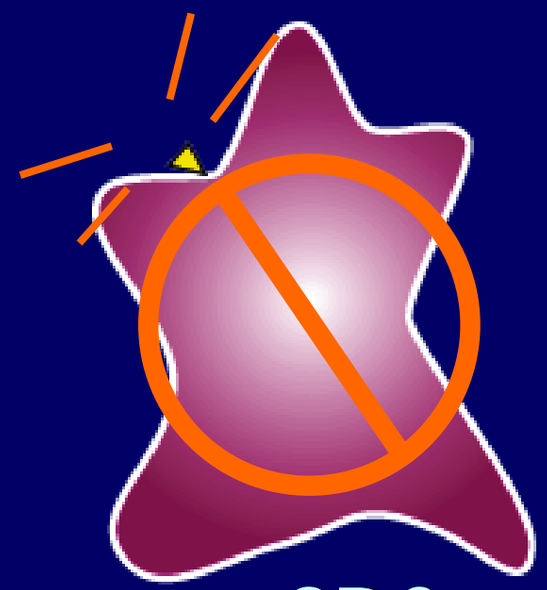
Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

NO HYDROXYLATION



2D6

= paroxetine
fluoxetine
high dose sertraline

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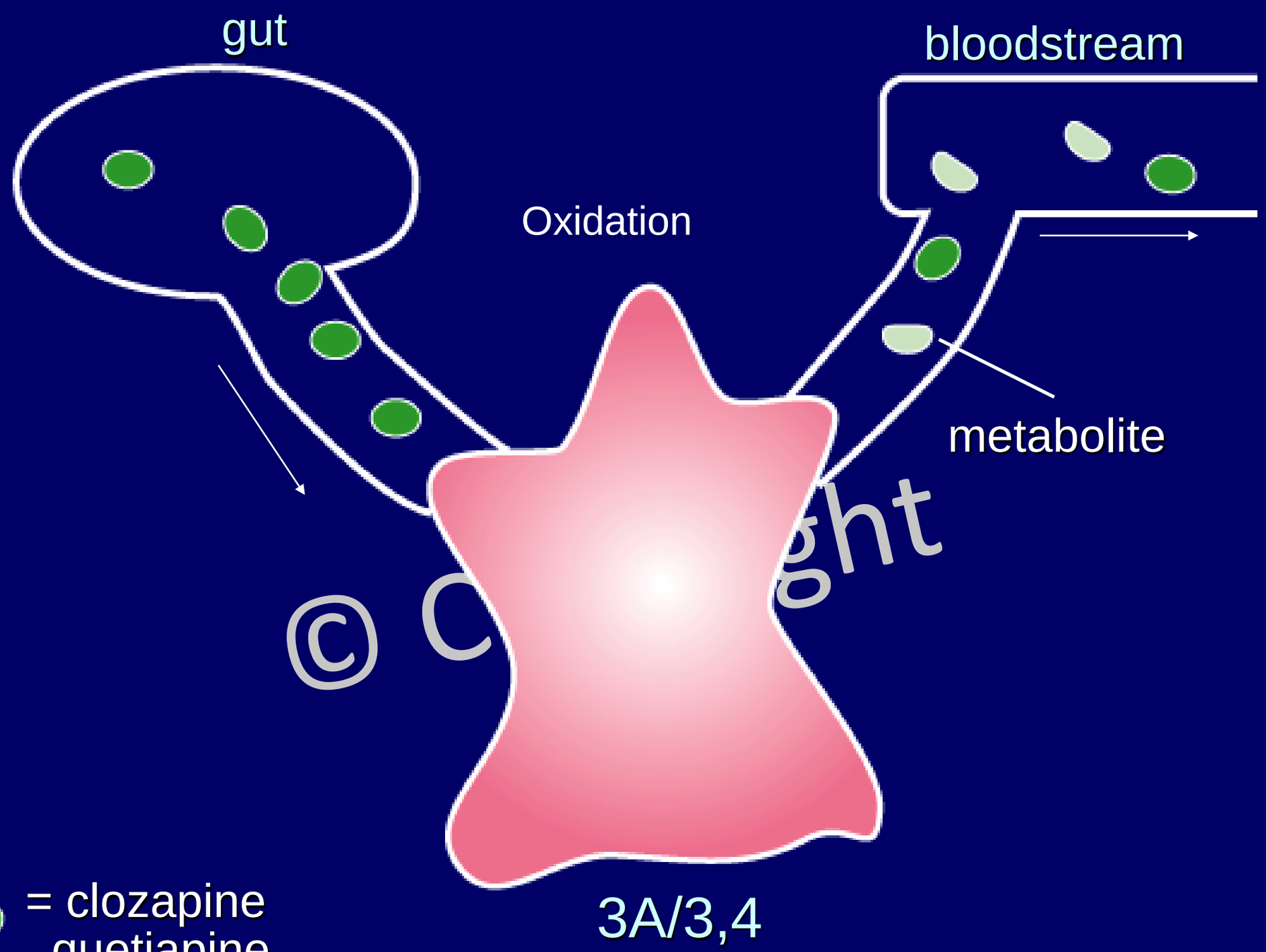
2D6

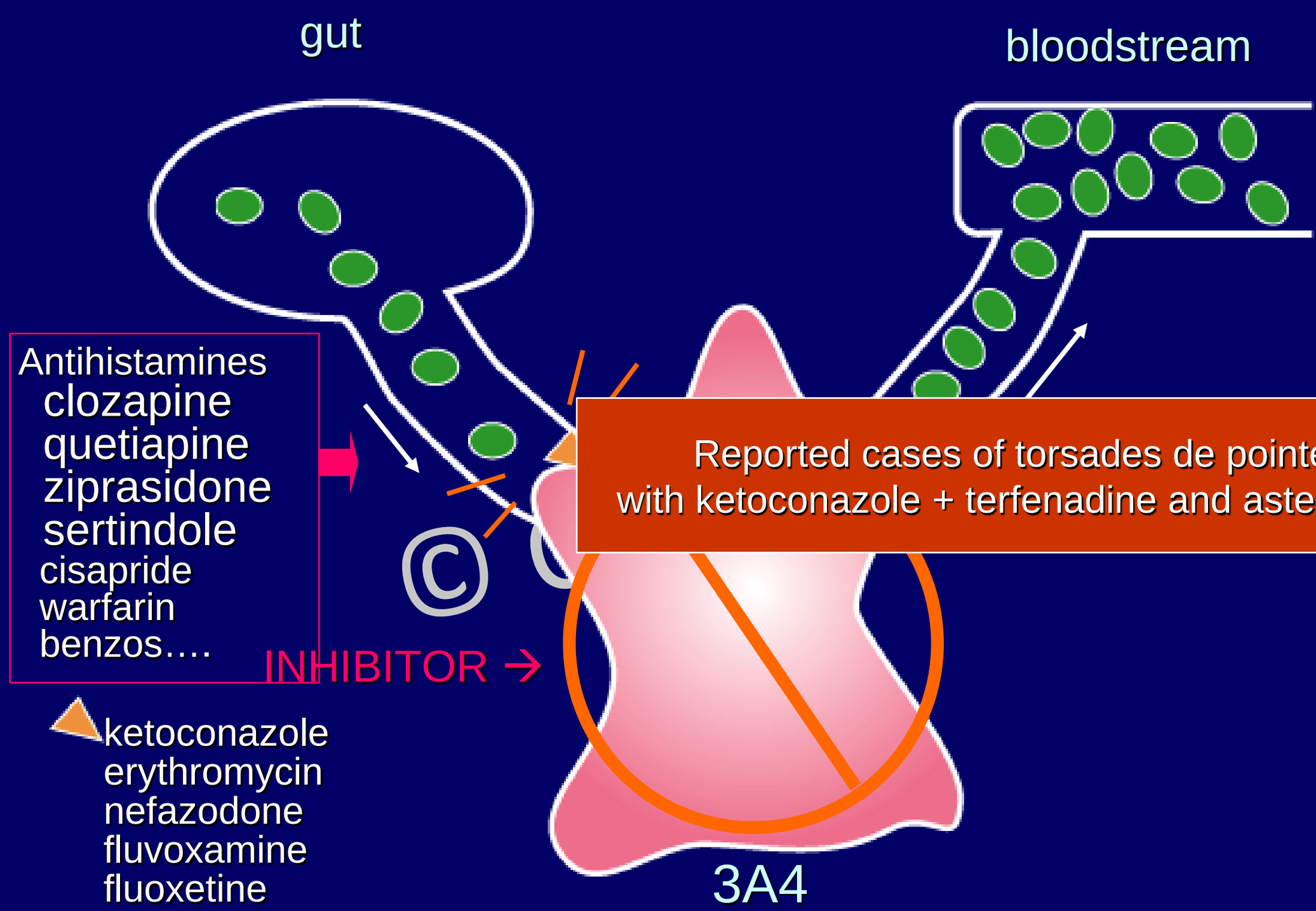
= clozapine
olanzapine
risperidone

Stahl S M, Essential Psychopharmaco (2000)



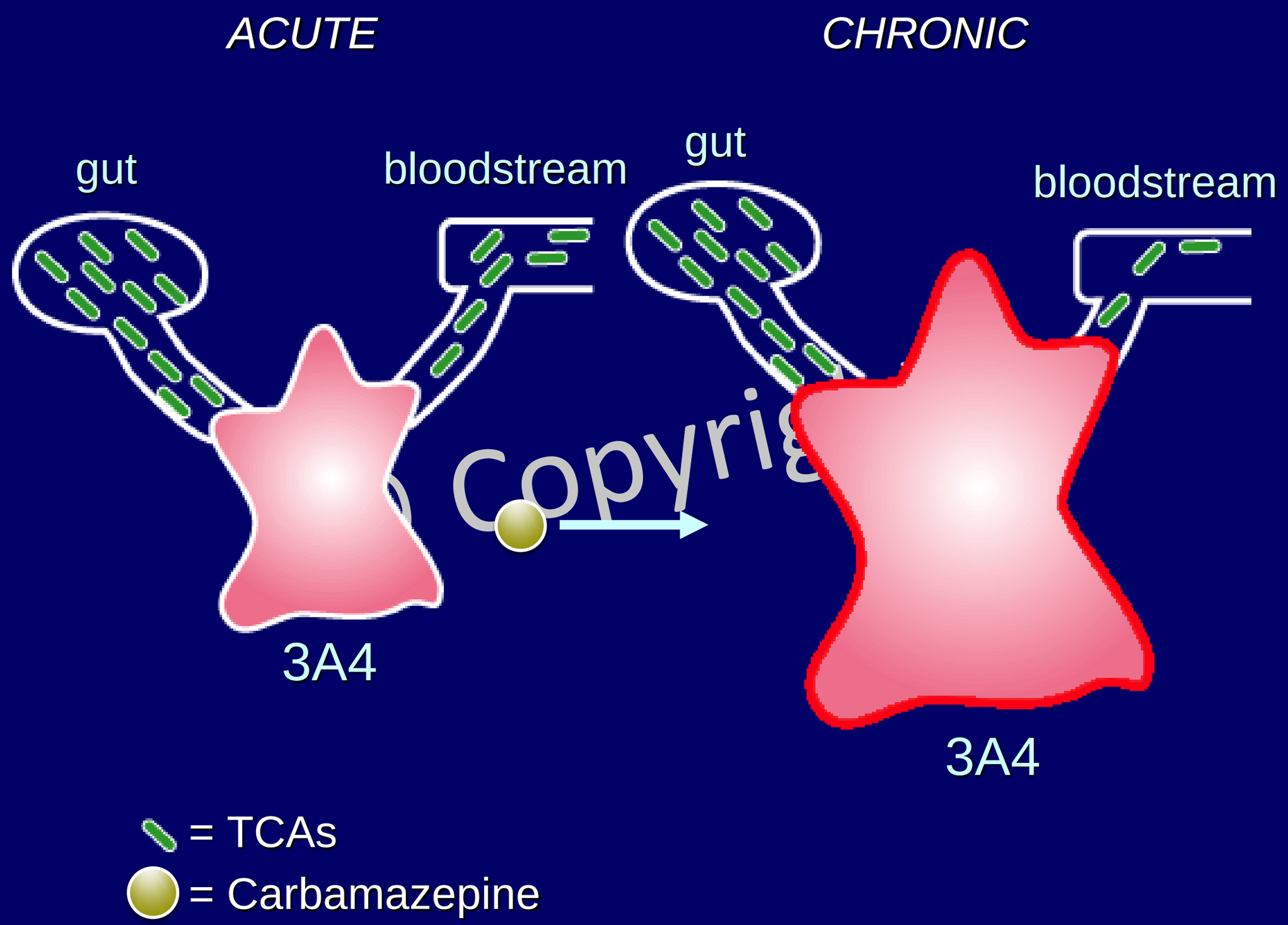
= clozapine
quetiapine
ziprasidone
sertindole

Stahl S M, Essential Psychopharmac

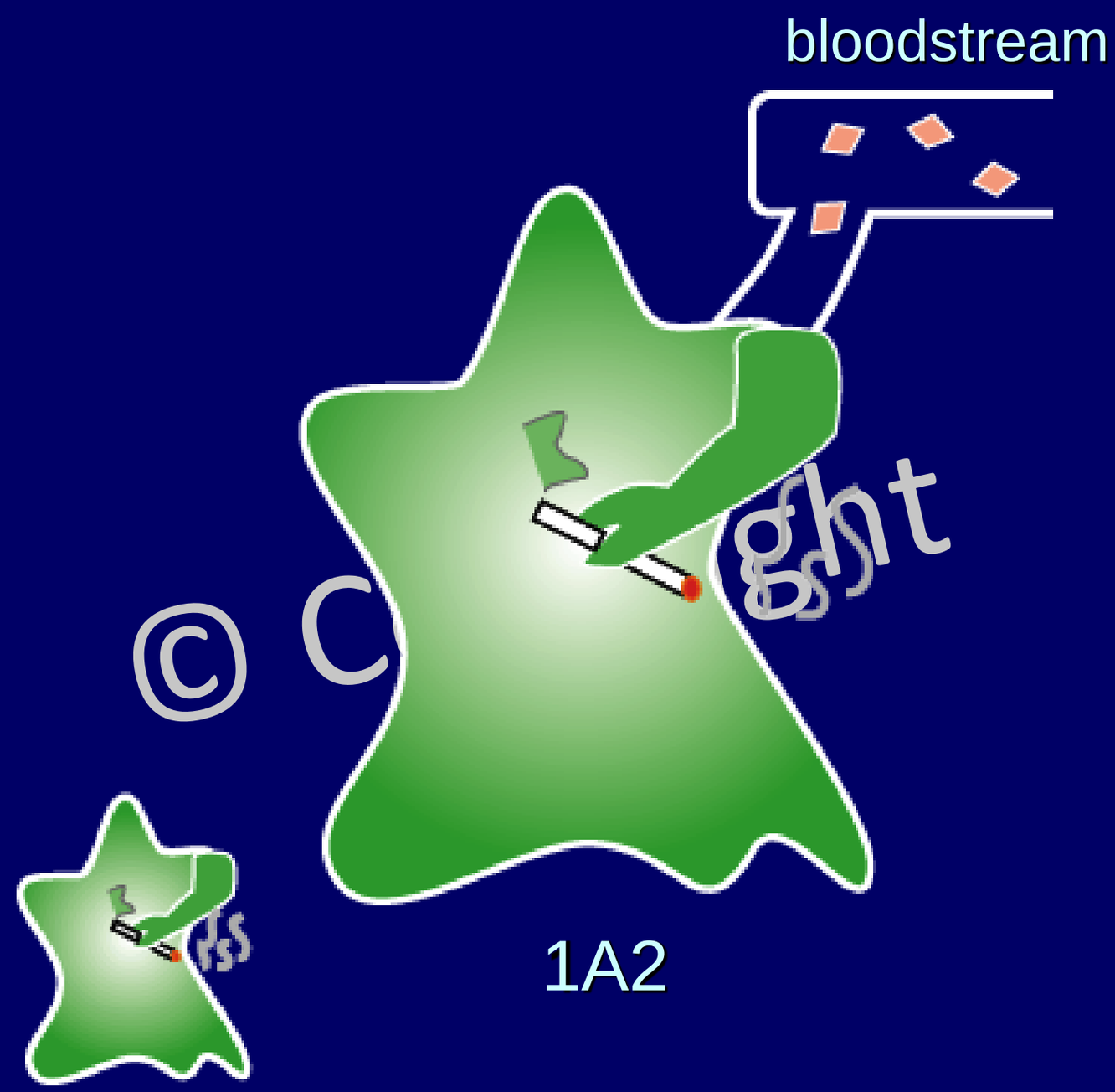


Reported cases of torsades de pointes with ketoconazole + terfenadine and astemizole

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



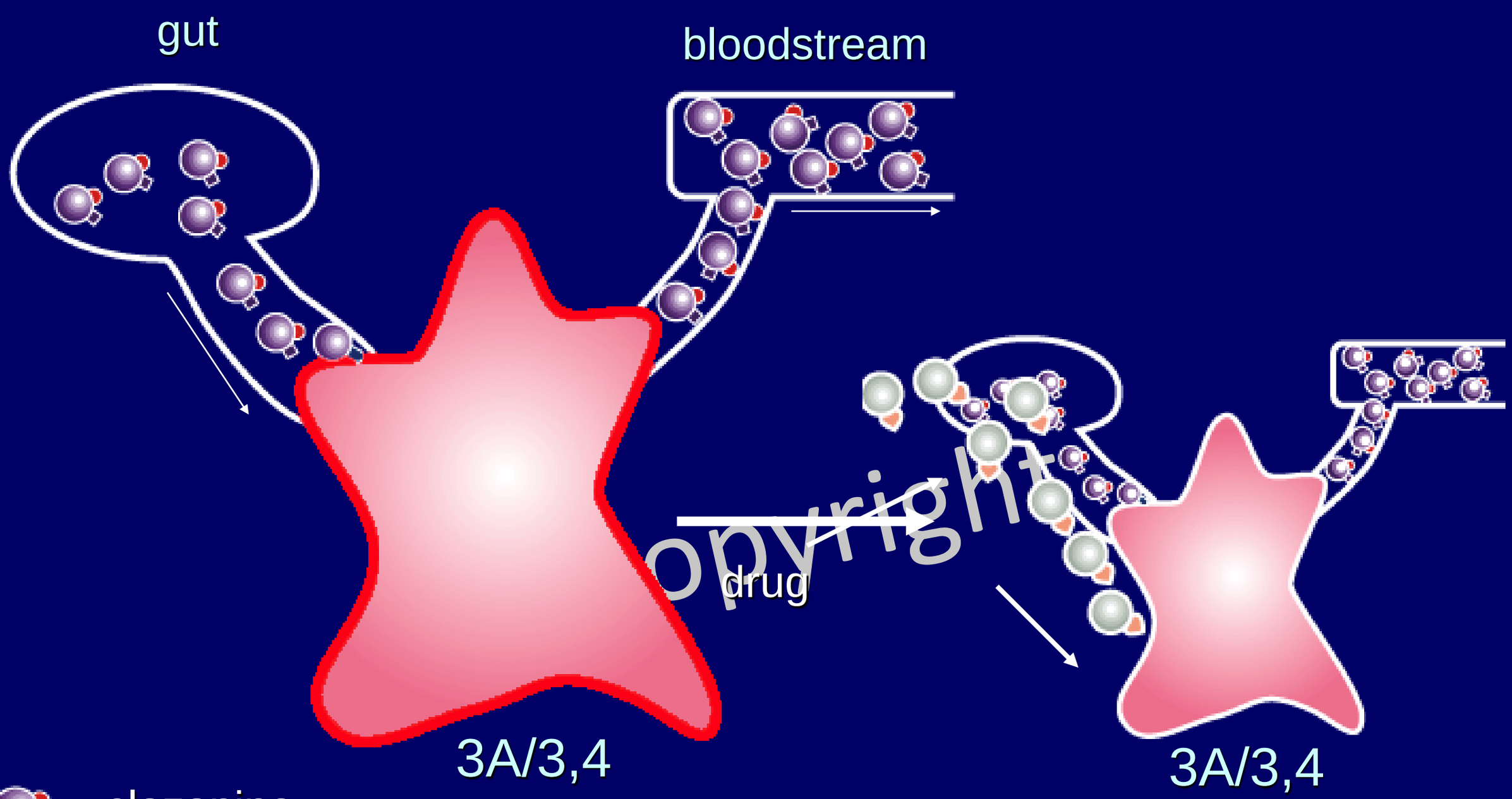
Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000

Six Possible Clinical Situations

Substrate	+	*Inhibitor*	= ↑	Substrate Levels
Inhibitor drug	+	Substrate	= ↑	Substrate Levels
Substrate	+	Inducer	= ↓	Substrate Levels
Inducer	+	Substrate	= ↓	Substrate Levels
Substrate	:	*Inhibitor*	= ↑	Substrate Metabolism Enhance the dose
Substrate	-	Inducer	= ↓	Substrate metabolism Taper the dose

Sandson, 2003. Drug Interactions, Case Book

Stahl, SM. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000



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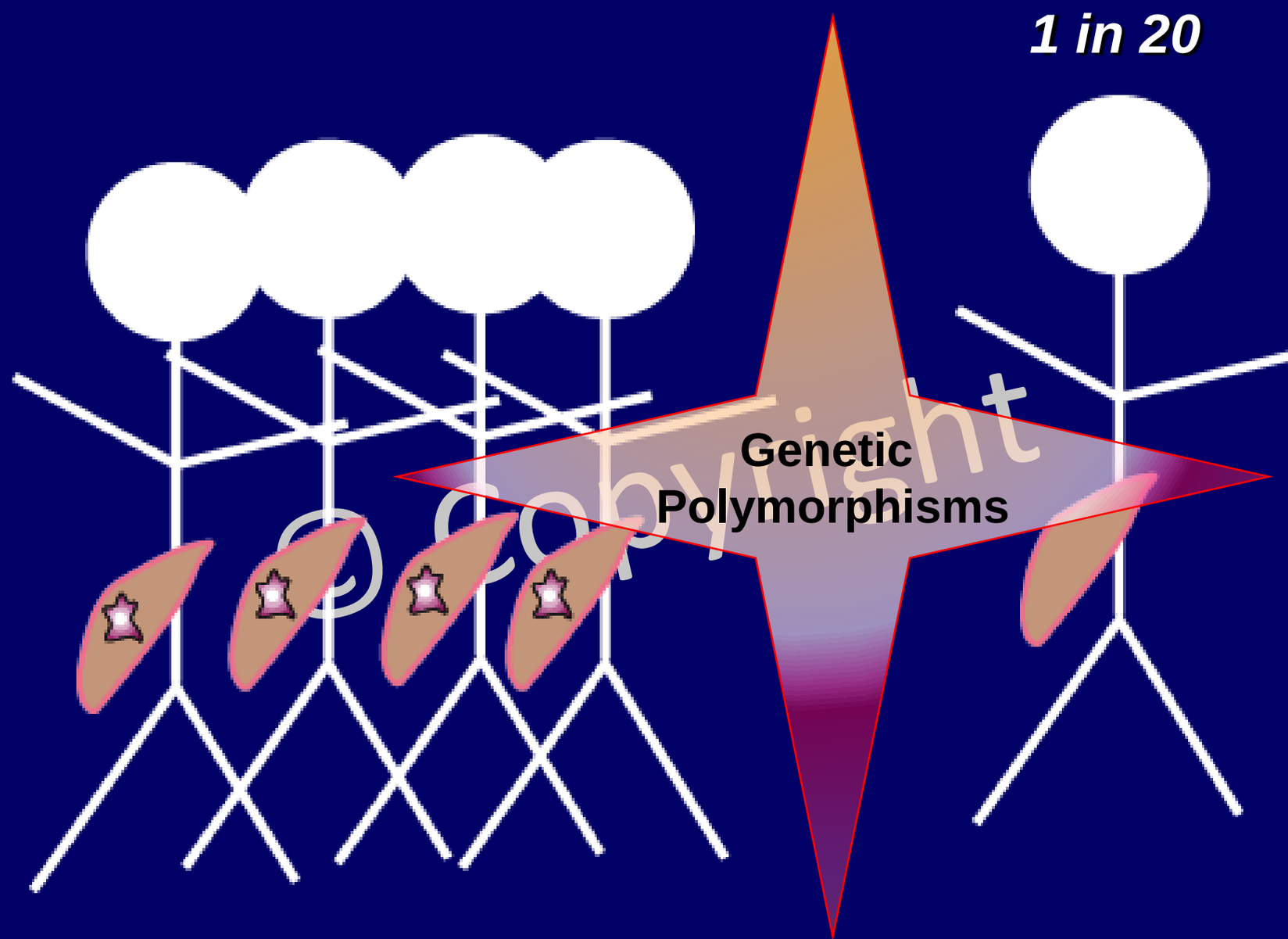
= clozapine
quetiapine
ziprasidone
sertindole

Stahl S M, Essential Psychopharmacology (2000)



genetic polymorphism for cytochrome P450 2D6

Stahl, S.M. Essential Psychopharmcaology. 2nd Edn. Cambridge, 2000