Narrow Therapeutic Index (NTI) Drugs: Definitions and Criteria
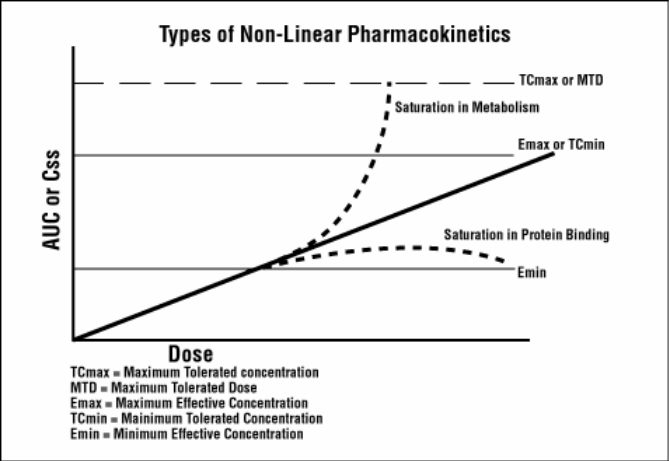
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Abstract

Purpose: Narrow therapeutic index (NTI) drugs must be routinely monitored for their severe effects. These drugs share some common features and criteria that focus on the separation of safety and efficacy in relation to toxicity and efficacy. Methods: There are many factors that contribute to drugs' high toxicity and lack of efficacy, including the following 5: right drug, right dose, right time, right duration, right age. Results: It's reviewed over 200 drugs, focusing on NTI drugs' clinical pharmacology, dose-response relationship, physiochemical properties, and potential drug-drug interactions. It is found that any minor change in therapeutic drug concentrations or doses may have significant consequences for patients, such as bleeding due to warfarin overdose or thrombotic events due to underdose. Conclusions: For NTI drugs, therapeutic drug monitoring (TDM) must be accessible in all hospitals and outpatient clinics to ensure patient safety. These approaches and methods must be done in each patient.
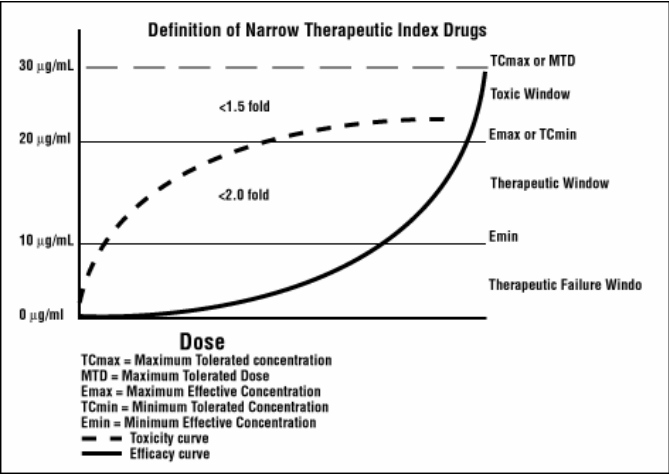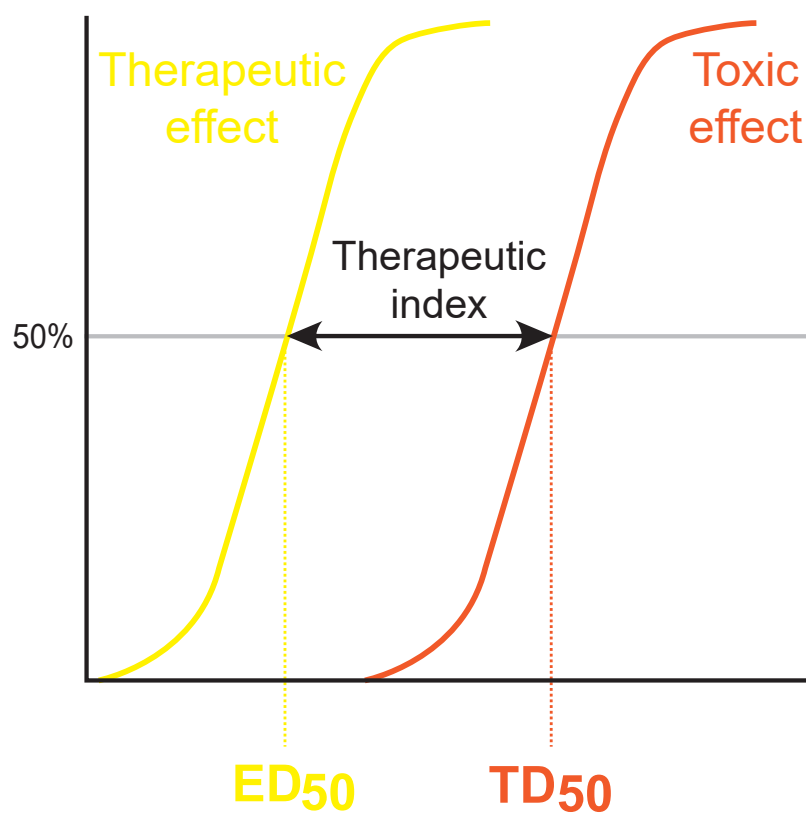
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NTI (Jan 3, 2023 BJCPT).doc available at https://authorea.com/users/469297/articles/617309-narrow-therapeutic-index-nti-drugs-definitions-and-criteria

Figure 1. Types of Non-Linear Pharmacokinetics. The solid line represents linear PK, the dotted line going up represents zero-order PK, and the dotted-line going down represents the saturation of plasma-protein binding.

Types of Non-Linear Pharmacokinetics

AUC or Css

TCmax or MTD

Saturation in Metabolism

Emax or TCmin

Saturation in Protein Binding

Emin

Dose

TCmax = Maximum Tolerated concentration
MTD = Maximum Tolerated Dose
Emax = Maximum Effective Concentration
TCmin = Mainimum Tolerated Concentration
Emin = Minimum Effective Concentration

Figure 2. Definition of Narrow Therapeutic Index (NTI) Drugs. The solid line represents Michaelis-Menten Kinetics and the dotted line represents non-linear PK.

Definition of Narrow Therapeutic Index Drugs

- 30 μg/mL — TCmax or MTD
- Toxic Window
- <1.5 fold
- 20 μg/ml — Emax or TCmin
- Therapeutic Window
- <2.0 fold
- 10 μg/mL — Emin
- Therapeutic Failure Windo
- 0 μg/ml

Dose

TCmax = Maximum Tolerated concentration
MTD = Maximum Tolerated Dose
Emax = Maximum Effective Concentration
TCmin = Minimum Tolerated Concentration
Emin = Minimum Effective Concentration
— — Toxicity curve
—— Efficacy curve

3

50%

Therapeutic effect

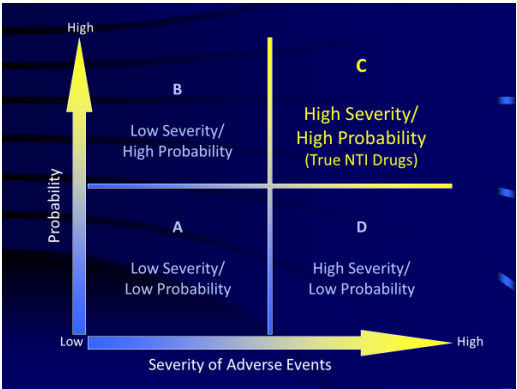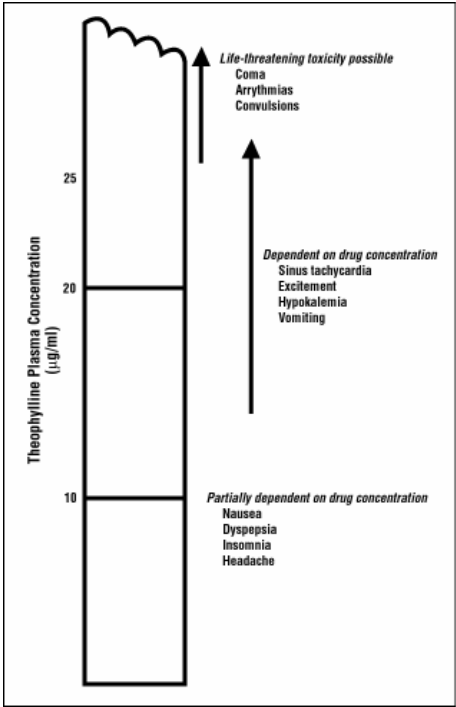Toxic effect

Therapeutic index

ED_{50} TD_{50}

Figure 4. Separation of Wide and Narrow Therapeutics Index Drugs. The first profile represents the therapeutic response the other profiles represent the adverse events.
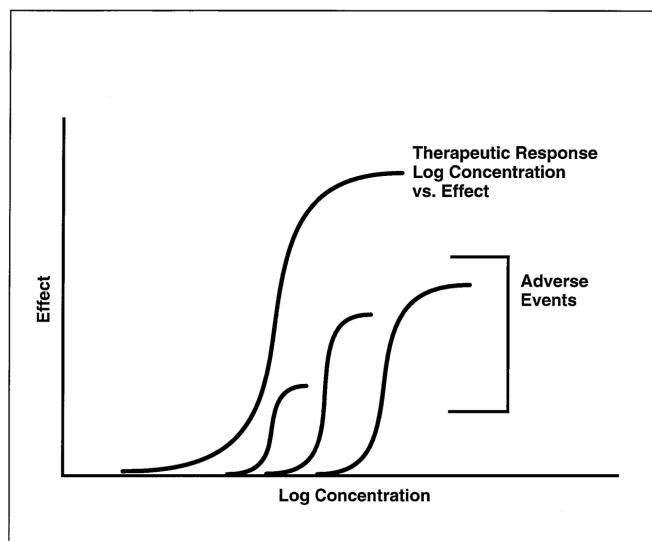
Figure 5.   The Four Quarters of Therapeutic Index (TI) Drugs. Quadrants A, B, C, D, represents low severity and low probability, low severity and high probability, high severity and high probability (true NTI Drugs), and high severity and low permeability, respectively.

Figure 7. Theophylline Plasma Concertation (mg/L) and Side Effect
(*adapted from T. Mant et al) in J, Henry and G. Volans Eds, ABC of poisoning.*
Part 1: Drugs. British Medical Association)

Figure 8.   Typical example of phenytoin toxicity at Steady-State and Non-linear
Pharmacokinetics (reproduced from the original paper)
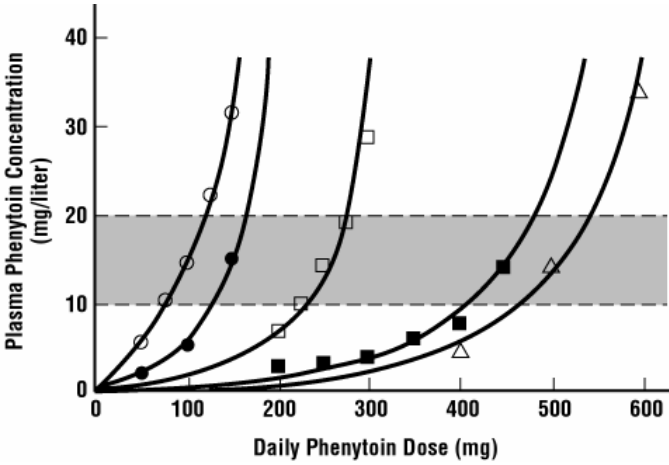
Figure 6.   Quantal Dose-Effect relationship. *Adapted with some modification from Katzung BG: Basic and clinical pharmacology, 5th edition. Appleton and Lange 1992)*

Characteristics of NTD5 (cont.)