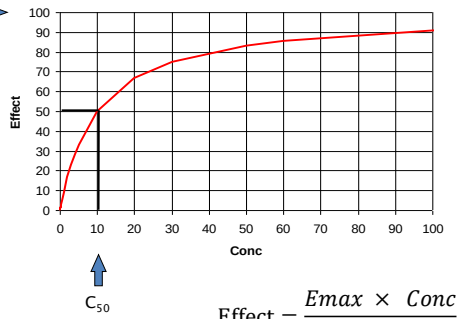
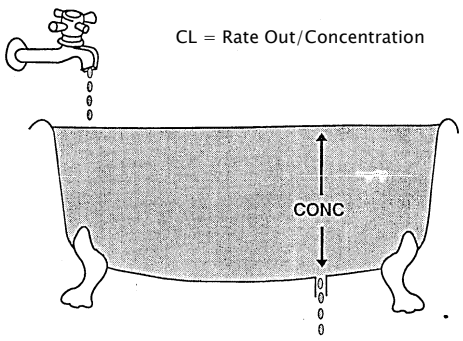
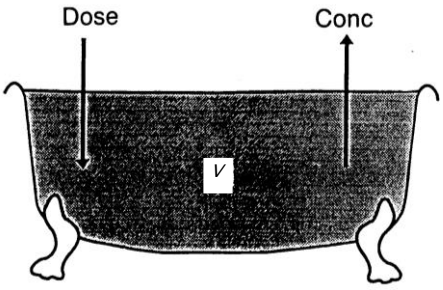
Slide 1	# The Target Concentration Approach to Dosing -- Application to Mycophenolate Nick Holford MBChB, FRACP Dept Pharmacology & Clinical Pharmacology University of Auckland New Zealand	
Slide 2	 ## Clinical Pharmacology Pharmacokinetics — Pharmacodynamics CL — V — Emax — C50 Dose — Concentration — Effect 	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).
Slide 3	 ## Conc and Effect Emax  C_{50} $\text{Effect} = \frac{Emax \times Conc}{C50 + Conc}$ 	http://clinpharmacol.fmhs.auckland.ac.nz/docs/immediate-time-course-of-drug-effect.pdf http://clinpharmacol.fmhs.auckland.ac.nz/docs/ligand-binding.pdf Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the C50 will be the same as the Kd (the equilibrium binding constant). Notice that Emax can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the C50 only reaches 90% of Emax.

Slide 4	 **Elimination Clearance**  	http://clinpharmacol.fmhs.auckland.ac.nz/docs/clearance.pdf The bathtub provides a physical model to explain how clearance determines drug elimination. This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time). Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state). Clearance is determined by the size of the hole in the bathtub.
Slide 5	 **Volume of Distribution** $V = \frac{Amount}{Conc}$  	http://clinpharmacol.fmhs.auckland.ac.nz/docs/volume-of-distribution.pdf The bathtub provides a physical model to explain how physical factors can influence the apparent volume. In this example there is no loss of water from the bathtub. By putting a known amount of drug (the dose) into the bathtub and measuring the concentration it is easy to calculate the apparent volume.
Slide 6	 **Target Concentration in Clinical Use of Medicines** **Target Conc = Target Effect x C50 / (Emax –Target Effect)** | Target Conc	Dose Model
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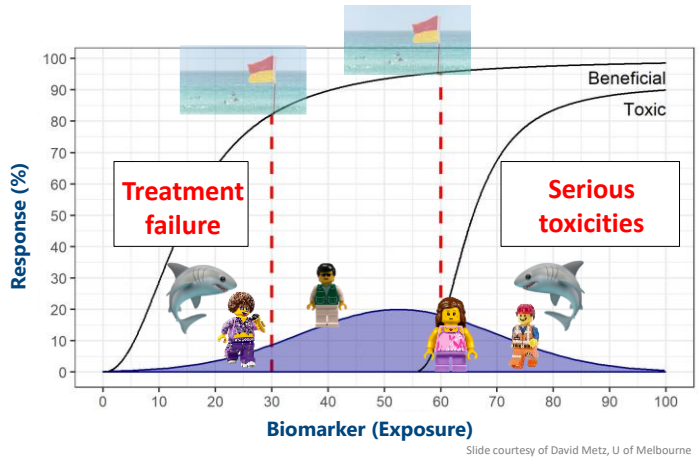
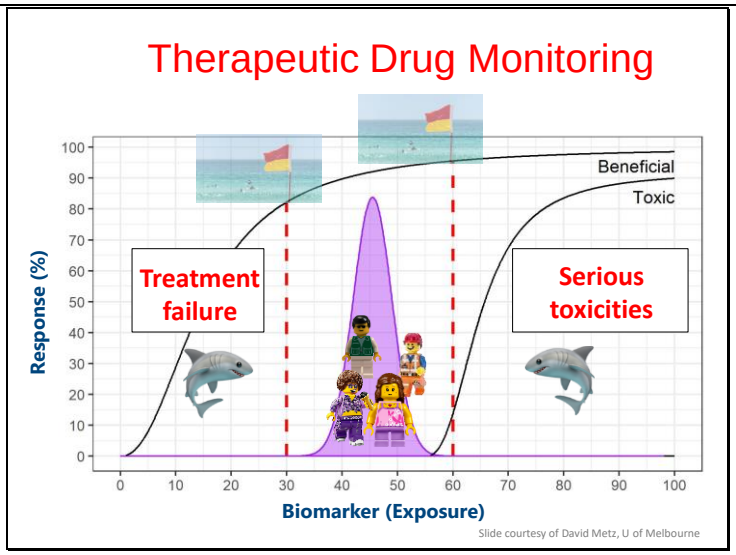
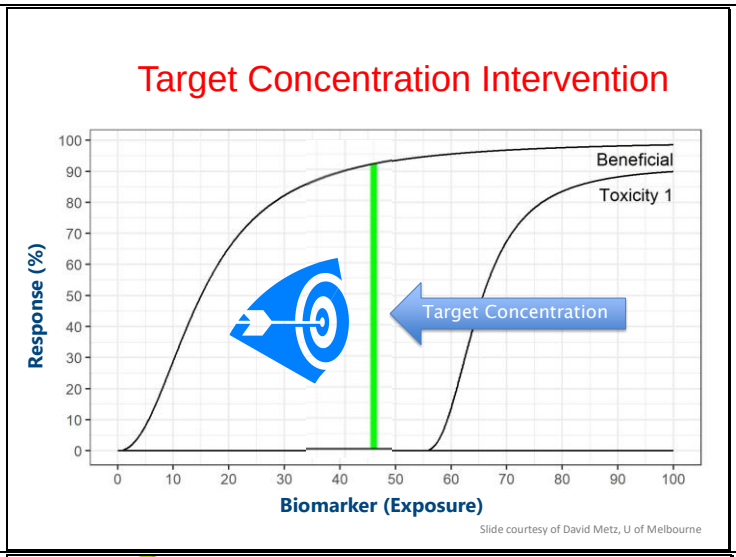
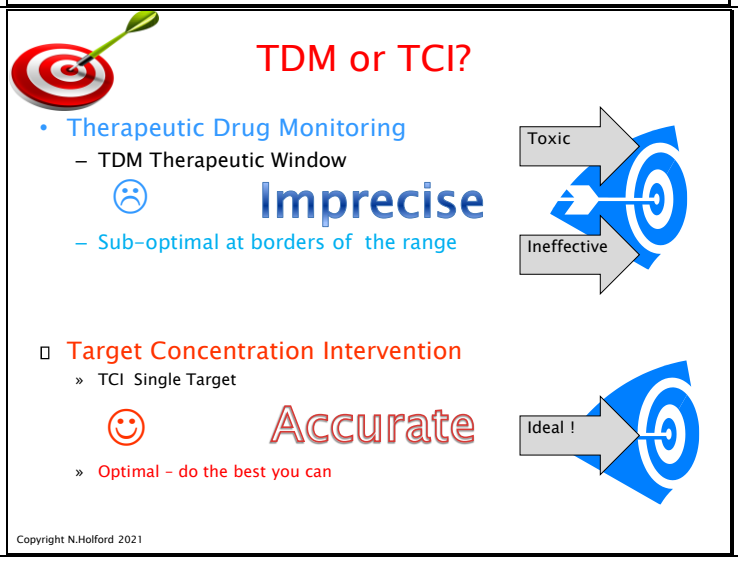
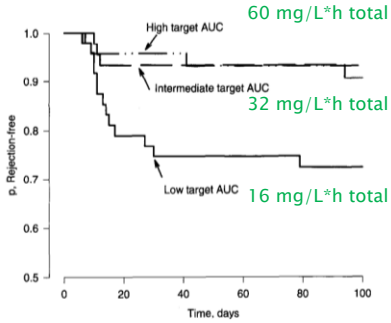
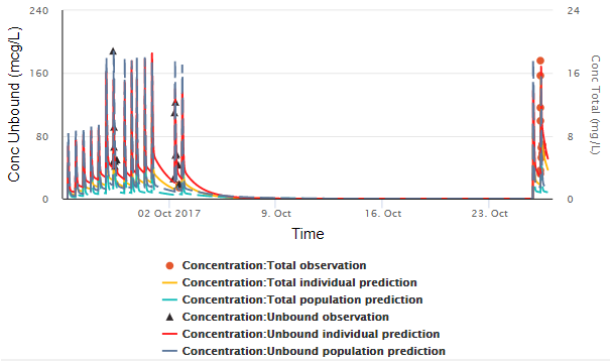
Initial Peak	Loading Dose = Target Conc x Volume of distribution
Average Steady State	Maintenance Dose Rate = Target Conc x Clearance | Ideal dose prediction requires **individual** estimates of **Emax, C50, Volume and Clearance** 	The target concentration approach links PKPD to prediction of the right dose for a patient.

Slide 7	 **Three Ways to Dose** • Population – Same dose for everyone • The dream dosing method! (often used in adults) • Group (Covariate guided) – Same dose for similar group • e.g. same weight, CLcr, genotype (usually used for children) • Individual – Dose determined by individual response • e.g. BP, INR, blood conc • concentration controlled dosing Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68. 	There are 3 ways to think about choosing the dose. The population dosing method uses the same dose for everyone. It is the most commonly used method but usually just for convenience. This means that some patients are either under-dosed or over-dosed. The group dosing method uses patient factors (also known as covariates) to predict the dose suitable for a group of patients with similar factors. Dosing in children is nearly always based on weight or age. The use of weight or renal function to adjust the dose is recommended for some medicines but probably not used as often as it should be. Individual dosing based on patient response is widely used when the response is easily measured. For example anti-hypertensive doses are usually adjusted based on the blood pressure response. The use of other response markers such as the international normalized ratio (INR) response to warfarin or the concentration of an antibiotic such as gentamicin are also examples. CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.
Slide 8	**Therapeutic Drug Monitoring**  Slide courtesy of David Metz, U of Melbourne	In the clinic patients will have exposure within, at the limit of, and outside the acceptable range. They will be distributed within and across the therapeutic window. The therapeutic drug monitoring approach, assumes, that all our patients sit within the flags. This assumption is not correct.

Slide 9		The second fallacy of TDM is what is done with a concentration measurement; what should be the magnitude of the dose change given a measured concentration? What should we do if the measurement is just inside or outside the acceptable range (e.g. 28 or 31 in this example)? Furthermore this approach assumes that there is a range of doses which match the acceptable range of concentrations. The maintenance dose rate is related to the target concentration and clearance. Clearance will time with time, but is constant at a single point in time. The target concentration can only be achieved by a single maintenance dose. It is not possible to have a range of targets (e.g. 28 to 31) as this will require a range of maintenance dose rates.
Slide 10		We can be more accurate and precise if we remove the flags and aim for a specific target. In the target concentration intervention approach, every measurement is used to guide dose adjustment to achieve a target concentration a measure which is correlated with improved outcomes. As described previously, maintenance dose rate is related to the target concentration and clearance. Therefore if we know the clearance for an individual, then the maintenance dose rate is known. Target concentration intervention also provides a method to link target concentration with dose. This means that the clinician is provided a proposed dose that will achieve the target.
Slide 11		http://clinpharmacol.fmhs.auckland.ac.nz/docs/target-concentration-intervention.pdf Note the difference between precision and accuracy. It is possible to have group shots at a target so that they are close together and thus precise – but not at the centre of the target. An accurate group of shots will be centred on the target. The term “precision dosing’ is not the same as “accurate dosing”. That is why target concentration intervention is a better description of individualized dosing method than precision dosing.

Slide 12	 **Why TDM Cannot Work** • TDM proposes a range of concentrations to judge if an individual is getting the right dose • It is not reasonable to prescribe a range of doses in order to match the range of concentrations • Therefore the therapeutic window cannot be used to get the right dose • There is only one dose that can achieve the target concentration that will produce the target effect 	
Slide 13	 **The Evidence – Tacrolimus** • TDM – Use of TDM had no effect in reducing renal transplant rejection • Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic window) • Anutrakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic window, more delayed graft function) TDM = goal was to reach exposure within therapeutic window in every patient. Clinicians were given dosing advice. 	Anutrakulchai S, Pongskul C, Kritmetapak K, Limwattananon C, Vannaprasaht S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol. 2019;85(9):1964-73. Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-6.
Slide 14	 **The Evidence – Vancomycin** • Three studies compared TCI with historical TDM • All showed TCI achieved more exposure in the therapeutic window than TDM • All showed reduced nephrotoxicity with TCI TCI = goal was to reach target AUC in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach target trough within therapeutic window in every patient. Clinicians may have been given dosing advice (varied by study). Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(4):433–42. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Internal Medicine Journal. 2012;42(1):23–9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62(2):e02042–17. 	Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(4):433-42. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Internal Medicine Journal. 2012;42(1):23-9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62(2):e02042-17.

Slide 15	 **The Evidence – Mycophenolate** • TCI – Use of TCI **reduced** renal transplant rejection • Hale 1998: Randomized Concentration Controlled Trial. 3 Target AUCs 16, 32, 60 mg/L*h ss 12h • Le Meur 2008 (APOMYGYRE): Fixed Dose vs Target AUC 40 mg/L*h ss 12h • TDM – Use of TDM had **no effect** in reducing renal transplant rejection • van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Window AUC 30–60 mg/L*h ss 12h • Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Window Trough >= 1.6 mg/L TCI = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach exposure within therapeutic window in every patient. Clinicians were not given dosing advice. Metz DK, Holford N, Kausman JY, Walker A, Cranswick N, Staatz CE, et al. Optimizing Mycophenolic Acid Exposure in Kidney Transplant Recipients: Time for Target Concentration Intervention. Transplantation. 2019;103(10):2012-30. Copyright N.Holford 2021	Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503. van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation. 2008;86(8):1043-51. Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. Am J Transplant. 2009;9(7):1607-19. Rousseau A, Laroche M-L, Venisse N, Loichot-Roselmac C, Turcant A, Hoizey G, et al. Cost-Effectiveness Analysis of Individualized Mycophenolate Mofetil Dosing in Kidney Transplant Patients in the APOMYGRE Trial. Transplantation. 2010;89(10):1255-62.
Slide 16	 **Mycophenolate Target** Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83.  **Figure 5.** Kaplan-Meier curves for freedom from rejection. Copyright N.Holford 2021	Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83.

Slide 17	 **Mycophenolate NextDose** http://www.nextdose.org **Observations** (dependent variables) available for calculation: Concentration Total, Concentration Unbound NextDose 1.7.5 Execution time: 4.8 s Run used actual data NextDose TCI mycophenolate 1650:2020-06-18-014154_conc_Metz2019_AVG **Target: CU 50 mcg/L at steady state** Perform another calculation Trapezoid AUC Units Interval Dose Pred Comment 2 419 mcg/L*h 0.0-6.1 maintenance dose 1433 mg AUC not reliable because sampling interval (6.1 h) is less than 75% of dosing interval (11.6 h) 4 489 mcg/L*h 0.0-8.6 maintenance dose 1227 mg AUC not reliable because sampling interval (8.6 h) is less than 75% of dosing interval (36.0 h) *Warning: Missing observation and imputed values (if any)* HTCM Height 192 cm WTKG.BSA (Boyd) Bayesian Route Predicted Dose Actual Dose 1 PO 475 mg mofetil every 12 hours 1000 mg mofetil 28/09/2017 07:27 2 PO 475 mg mofetil every 12 hours 1000 mg mofetil 28/09/2017 13:45 3 PO 987 mg mofetil every 12 hours 1000 mg mofetil 02/10/2017 07:50 4 PO 987 mg mofetil every 12 hours 1000 mg mofetil 02/10/2017 16:55 5 PO 987 mg mofetil every 12 hours 1000 mg mofetil 26/10/2017 12:25 **Proposed PO maintenance dose 782 mg mofetil every 12 hours (Bayesian Average)** *Warning: A predicted dose differs from actual dose by more than 50% (-53%). Check input data carefully before using proposed dose.* Metz & Holford ADOPT 2019 0-3 months post transplant CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation and follow-up is recommended especially for trough concentration targets. CL L/h fCL% V L fV% F fF% FFM kg RF% ALB g/L fu MPA % 757 -27.4 3263 7.7 0.950 0 66.1 14.7 32.0 1.66 750 -28.1 3078 1.6 0.950 0 66.1 14.7 32.0 1.66 1449 -33.3 3264 7.8 0.950 0 66.1 14.7 31.0 1.71 1576 -27.4 3995 31.9 0.950 0 66.1 14.7 31.0 1.76 1229 -43.4 2947 -2.7 0.950 0 66.1 14.7 33.0 1.38 Copyright N.Holford 2021	NextDose target concentration intervention report for a patient after treatment with mycophenolate. The trapezoidal AUC and dose predicted from the AUC are shown only to compare with the Bayesian predicted dose which is expected to be more reliable.
Slide 18	 **Mycophenolate NextDose** http://www.nextdose.org  Copyright N.Holford 2021	The measured unbound and total concentrations are shown with population predictions based on the dose, age and size. Predictions of concentrations are shown along with observed values.
Slide 19	 **Conclusion** Received: 6 February 2020 | Revised: 28 April 2020 | Accepted: 19 May 2020 DOI: 10.1111/bcp.14434 **REVIEW-THEMED ISSUE** **TDM is dead. Long live TCI!** Nick Holford[1] | Guangda Ma[1] | David Metz[2] Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J ClinPharmacol. 2020; (doi:10.1111/bcp.14434). Copyright N.Holford 2021	Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020; Early View (doi:10.1111/bcp.14434).