Predictive Performance of the Winter-Tozer and Its Derivative Equations for Estimating Free Phenytoin Concentrations in Neurology Patients on Concurrent Enzyme Inducers (Phenobarbital, Carbamazepine) and Inhibitors (Valproic Acid)

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Background

- Phenytoin (PHT) highly bound to albumin
- Efficacy & toxicity determined by free concentration
- Protein binding affected by drug interactions
- Most commonly used equation:
  - Winter-Tozer: poor predictive performance, developed in absence of interacting drugs
- Valproic acid (VPA) interaction studied in literature
  - Two equations developed, lacked hypoalbuminemic patients
  - VPA displaces PHT from albumin, inhibits PHT metabolism
- Carbamazepine (CBZ) likely induces CYP2C19
- Phenobarbital (PB) induces CYP2C9 and CYP3A4 enzymes
- No equations developed to account for CBZ, PB interactions

Methods

- Retrospective chart review at Vancouver General Hospital from Aug 2005 – Aug 2014
- Convenience sample ~30 patients per interacting medication (VPA, PB, CBZ)
- Inclusion: ≥ 18 years old, steady state PHT free & total concentrations
- Exclusion: Hemodialysis, pregnancy
- Mean prediction error (MPE) to assess bias and root mean square error (RMSE) to assess precision
- Primary objective:
  - To assess the accuracy and precision of the Winter-Tozer equation and other identified equations in estimating free phenytoin concentrations in neurology patients taking concurrent enzyme inducers/inhibitors

Exclusion Flow Chart

1112 patient account numbers with PHT and/or interacting drug orders from Aug 2005 – Aug 2014

967 patient account numbers excluded:
- Duplicate patients (n=21)
- No free PHT level (n=650)
- PHT level not at steady state (n=39)
- No VPA level for patients in VPA group (n=91)
- Albumin level not drawn within 24 hours of PHT level (n=151)
- Patient not at VGH (n=14)
- Hemodialysis patient (n=1)

145 patient account numbers (132 different patient charts reviewed)

89 patients excluded:
- PHT level not at steady state (n=73)
- Level drawn early (<6h after dose) (n=3)
- Did not receive both drugs together (n=10)
- Chart not accessible (confidential n=2, offsite n=1)

44 PHT levels included for analysis (43 patients)

Table 1: Summary of Baseline Characteristics

Characteristic Mean (SD)	All (n=44)	Valproic Acid (n=15)	Carbamazepine (n=22)	Phenobarbital (n=9)
Age (years)	57.2 (27.0)	56.6 (19.8)	52.3 (20.3)	68.7 (17.0)
Male (n,%)	27(61%)	8 (53%)	14 (64%)	7 (78%)
SCr (µmol/L)	64.8 (21.4)	52.9 (16.4)	69.2 (21.4)	75.1 (19.7)
Albumin ≤ 34 g/L (n,%)	31 (70%)	14 (93%)	15 (68%)	4 (44%)

Predictive Equations

Equation 1 (Winter-Tozer)[1]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.2 \times \text{Albumin} + 0.1)} \times 0.1$$

Equation 2* (May et al.)[2]

$$\text{Predicted Free PHT} = [0.0792 + (0.000636 \times \text{VPA})] \times \text{Measured Total PHT}$$

Equation 3* (Haidukewych et al.)[3]

$$\text{Predicted Free PHT} = [0.095 + (0.001 \times \text{VPA})] \times \text{Measured Total PHT}$$

Equation 4 (Kane et al.)[4]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.29 \times \text{Albumin} + 0.1)} \times 0.1$$

Equation 5 (Kane et al.)[4]

$$x = -0.40378 + (\text{Measured Total PHT} \times 0.17807) + (-0.00328 \times \text{Measured Total PHT}^2) + (-0.31312 \times \text{Albumin}) + (0.12362 \times \text{Male}) + (-0.00174 \times \text{CrCl})$$

$$\text{Predicted Free PHT} = e^x$$

Equation 6 (Cheng et al.)[5]

$$\text{Predicted Free PHT} = \frac{\text{Measured Total PHT}}{(0.275 \times \text{Albumin} + 0.1)} \times 0.1$$

$$\text{MPE} = \frac{1}{n}\sum \text{PE}$$

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum (\text{PE})^2}$$

* CBZ, PB substituted for VPA in applicable subgroups

Phenytoin (PHT) in µg/mL (x 4 to get µmol/L)
Albumin in g/dL (x 10 to get g/L)
VPA in µg/mL (x 6.94 to get µmol/L)
CBZ in µg/mL (x 4.23 to get µmol/L)
PB in µg/mL (x 4.31 to get µmol/L)
PE = predictive error

[1] Applied Therapeutics. 1992;25.1-25.44.
[2] Eur Neurol. 1991;31: 57-60.
[3] Ther Drug Monit. 1989;11:134-9.
[4] Ann Pharmacother. 2013;47:628-36.
[5] Pharmacotherapy. (Abstract). 2014;34: #144 (p. e214) DOI: 10.1002/phar.1497

Table 2: Bias and Precision by Interaction

Equation	All (n=44)	VPA (n=15)	CBZ (n=22)	PB (n=9)
Bias (MPE) (95%CI) (µmol/L)				
1	**1.3** (0.8 to 1.8)	**0.2** (-0.6 to 1.0)	**2.1** (1.5 to 2.7)	**0.8** (-0.6 to 2.2)
2	**-1.8** (-2.5 to -1.1) *(n=30)*	**-2.1** (-3.5 to -0.7)	**-0.7** (-1.8 to 0.4) *(n=10)*	**-2.9** (-4.8 to -1.0) *(n =5)*
3	**-0.6** (-1.3 to 0.1) *(n=30)*	**-0.6** (-1.9 to 0.7)	**0.2** (-1.0 to 1.4) *(n=10)*	**-0.7** (-3.3 to 1.9) *(n =5)*
4	**-0.9** (-1.4 to -0.4)	**-1.8** (-2.9 to -0.7)	**0.0** (-0.4 to 0.4)	**-1.8** (-3.1 to -0.5)
5	**-1.2** (-1.9 to -0.5)	**-1.9** (-3.0 to -0.8)	**-0.1** (-0.5 to 0.3)	**-2.7** (-5.2 to -0.2)
6	**-0.6** (-1.1 to -0.1)	**-1.6** (-2.6 to -0.6)	**0.3** (-0.1 to 0.7)	**-1.5** (-2.8 to -0.2)
Precision (RMSE) (95%CI)				
1	**2.2** (0.0 to 4.4)	**1.5** (-0.6 to 3.6)	**2.5** (-1.3 to 6.3)	**2.2** (-2.1 to 6.5)
2	**3.2** (-3.8 to 10.2) *(n=30)*	**3.4** (-11.9 to 18.7)	**1.8** (-2.9 to 6.5) *(n=10)*	**3.9** (-13.7 to 21.5) *(n =5)*
3	**2.6** (-2.3 to 7.5) *(n=30)*	**2.6** (-7.4 to 12.6)	**1.8** (-1.6 to 5.2) *(n=10)*	**3.6** (-10.0 to 17.2) *(n =5)*
4	**2.1** (-1.2 to 5.4)	**2.7** (-5.8 to 11.2)	**0.9** (0.3 to 1.5)	**2.6** (-5.4 to 10.6)
5	**2.7** (-3.5 to 8.9)	**2.9** (-6.6 to 12.4)	**0.9** (0.5 to 1.3)	**4.5** (-20.9 to 29.9)
6	**1.9** (-1.0 to 4.8)	**2.5** (-5.0 to 10.0)	**1.0** (0.3 to 1.7)	**2.3** (-5.2 to 9.8)

Table 3: Bias and Precision by Age

MPE (µmol/L)/ RMSE (95% CI)	Equation 1	Equation 2	Equation 3	Equation 4	Equation 5	Equation 6
≤ 60 years (n= 24)	**1.6** (0.8 to 2.4)	**-1.2** (-1.9 to -0.5) *(n=18)*	**0.3** (-0.5 to 1.1) *(n=18)*	**-0.7** (-1.3 to -0.1)	**-1.1** (-2.1 to -0.1)	**-0.4** (-1.0 to 0.2)
	2.5 (-1.1 to 6.1)	**1.9** (-1.1 to 4.9) *(n=18)*	**1.7** (0.6 to 2.8) *(n=18)*	**1.7** (-0.7 to 4.1)	**2.8** (-7.0 to 12.6)	**1.6** (-0.5 to 3.7)
> 60 years (n= 20)	**0.8** (0.0 to 1.6)	**-2.7** (-4.6 to -0.8) *(n=12)*	**-1.4** (-3.3 to 0.5) *(n=12)*	**-1.2** (-2.2 to -0.2)	**-1.4** (-2.4 to -0.4)	**-0.9** (-1.8 to 0.0)
	1.9 (-0.2 to 4.0)	**4.3** (-16.3 to 24.9) *(n=12)*	**3.5** (-10.8 to 17.8) *(n=12)*	**2.4** (-4.5 to 9.3)	**2.7** (-4.9 to 10.3)	**2.3** (-3.8 to 8.4)

Figure 1: Bland-Altman Plots for All Patients, Carbamazepine, Phenobarbital, and Valproic Acid

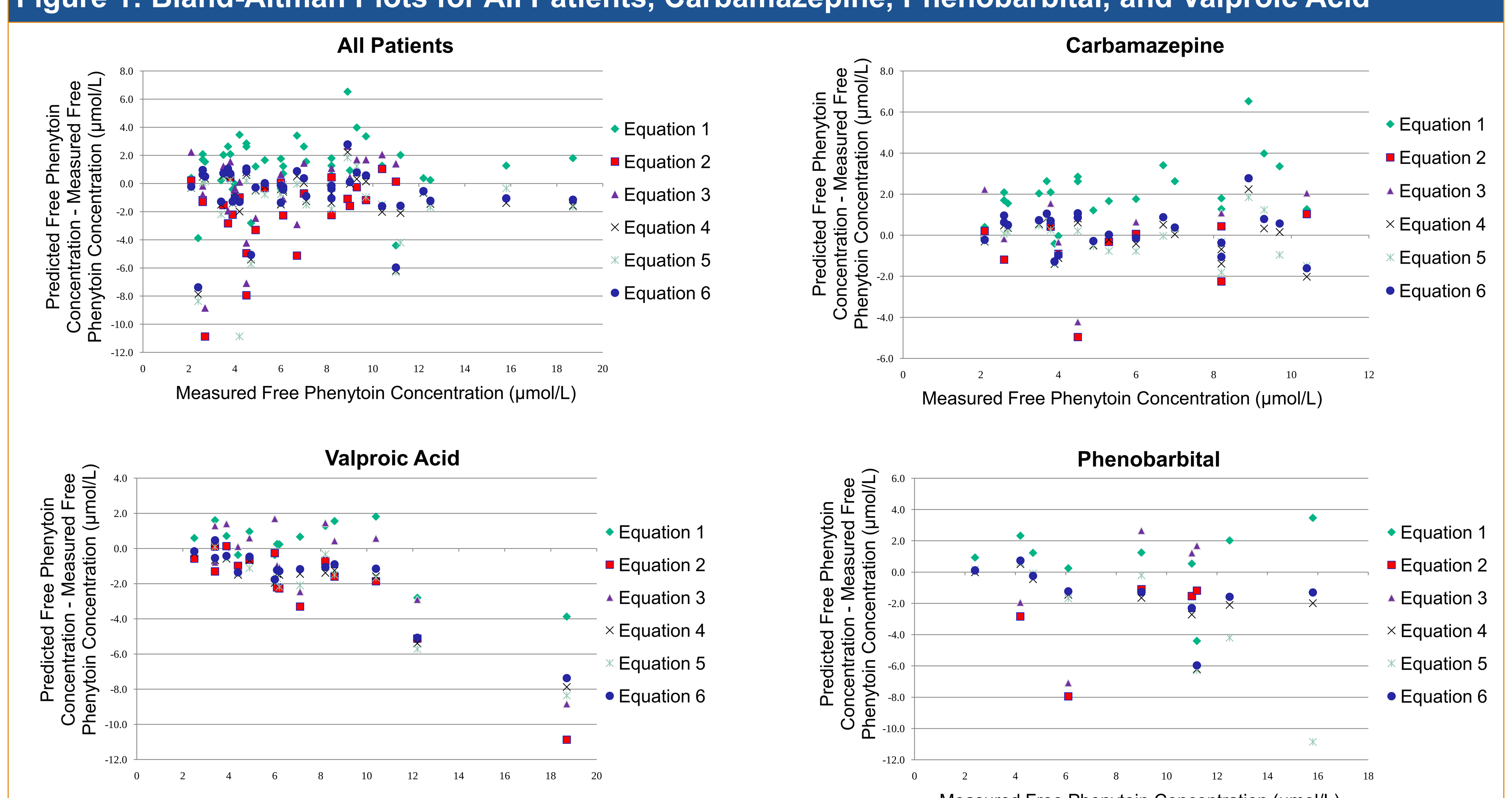

Table 4: Bias and Precision for Subgroups based on CYP interaction, dose, eGFR

MPE (µmol/L)/ RMSE (95% CI)	Equation 1	Equation 2	Equation 3	Equation 4	Equation 5	Equation 6
CYP interaction (n= 19)	**0.8** (0.0 to 1.6)	**-2.8** (-4.6 to -1.0) *(n=13)*	**-1.4** (-3.2 to 0.4) *(n=13)*	**-1.3** (-2.3 to-0.3)	**-1.3** (-2.3 to-0.3)	**-1.1** (-2.0 to -0.2)
	2.0 (-0.2 to 4.2)	**4.2** (-14.8 to 23.2) *(n=13)*	**3.5** (-9.6 to 16.6) *(n=13)*	**2.5** (-4.5 to 9.5)	**2.6** (-5.2 to 10.4)	**2.4** (-3.9 to 8.7)
No CYP interaction (n= 25)	**1.6** (0.9 to 2.3)	**-1.0** (-1.7 to -0.3) *(n=17)*	**0.4** (-0.3 to 1.1) *(n=17)*	**-0.6** (-1.2 to 0.0)	**-1.2** (-2.2 to -0.2)	**-0.3** (-0.9 to 0.3)
	2.4 (-1.1 to 5.9)	**1.8** (-1.2 to 4.8) *(n=17)*	**1.6** (0.4 to 2.8) *(n=17)*	**1.6** (-0.7 to 3.9)	**2.8** (-6.6 to 12.2)	**1.5** (-0.5 to 3.5)
Total Daily PHT dose <300 mg (n= 5)	**1.3** (0.7 to 1.9)	**-1.0** (-2.2 to 0.2) *(n=4)*	**0.3** (-0.6 to 1.2) *(n=4)*	**-0.5** (-1.3 to 0.3)	**-0.9** (-1.8 to 0.0)	**-0.3** (-1.1 to 0.5)
	1.5 (0.0 to 3.0)	**1.4** (-0.9 to 3.7) *(n=4)*	**0.8** (0.3 to 1.3) *(n=4)*	**1.0** (0.2 to 1.8)	**1.3** (-0.4 to 3.0)	**0.8** (0.3 to 1.3)
300 mg (n=13)	**0.4** (-0.6 to 1.4)	**-3.3** (-5.9 to -0.7) *(n=8)*	**-2.1** (-4.4 to 0.2) *(n=8)*	**-1.5** (-2.8 to -0.2)	**-1.6** (-3.0 to -0.2)	**-1.3** (-2.6 to 0.0)
	1.8 (-0.5 to 4.1)	**4.8** (-23.0 to 32.6) *(n=8)*	**3.8** (-14.6 to 22.2) *(n=8)*	**2.8** (-7.0 to 12.6)	**3.0** (-8.5 to 14.1)	**2.6** (-6.0 to 11.2)
301-499 mg (n= 17)	**1.3** (0.4 to 2.2)	**-1.3** (2.5 to -0.1) *(n=13)*	**0.0** (-1.4 to 1.4) *(n=13)*	**-0.9** (-1.7 to -0.1)	**-1.7** (-3.1 to -0.3)	**-0.6** (-1.4 to 0.2)
	2.3 (-0.3 to 4.9)	**1.1** (-8.2 to 10.4) *(n=13)*	**1.0** (-6.3 to 8.3) *(n=13)*	**1.8** (-2.6 to 6.2)	**3.3** (-10.6 to 17.2)	**1.7** (-2.3 to 5.7)
≥500 mg (n= 9)	**2.4** (1.1 to 3.7)	**-1.2** (-2.1 to -0.3) *(n=5)*	**0.9** (-0.2 to 2.0) *(n=5)*	**-0.3** (-1.3 to 0.7)	**0.0** (-0.9 to 0.9)	**0.0** (-1.0 to 1.0)
	3.0 (-5.8 to 11.8)	**1.5** (-0.3 to 3.3) *(n=5)*	**1.4** (-0.2 to 3.0) *(n=5)*	**1.5** (-0.1 to 3.1)	**1.3** (0.3 to 2.3)	**1.5** (-0.2 to 3.2)
eGFR 30-59 mL/min (n=3)	**1.4** (0.8 to 2.0)	N/A	N/A	**-0.9** (-2.1 to 0.3)	**-1.5** (-4.2 to 1.2)	**-0.6** (-1.6 to 0.4)
	1.5 (-0.4 to 3.4)	N/A	N/A	**1.2** (-1.6 to 4.0)	**2.4** (-9.0 to 13.8)	**0.9** (-0.7 to 2.5)
60-89 mL/min (n=8)	**0.8** (0.1 to 1.5)	**-1.0** (-1.9 to -0.1) *(n=4)*	**0.3** (-0.7 to 1.3) *(n=4)*	**-0.8** (-1.4 to -0.2)	**-0.5** (-1.0 to 0.0)	**-0.6** (-1.2 to 0.0)
	1.2 (0.2 to 2.2)	**1.3** (-1.0 to 3.6) *(n=4)*	**0.9** (0.0 to 1.8) *(n=4)*	**1.2** (0.5 to 1.9)	**0.8** (0.2 to 1.4)	**1.0** (0.5 to 1.5)
>90 mL/min (n= 33)	**1.3** (0.6 to 2.0)	**-1.9** (-3.0 to -0.8) *(n=25)*	**-0.6** (-1.7 to 0.5) *(n=25)*	**-0.9** (-1.6 to -0.2)	**-1.4** (-2.3 to -0.5)	**-0.7** (-1.4 to 0.0)
	2.5 (-0.3 to 5.3)	**3.3** (-7.0 to 13.6) *(n=25)*	**2.8** (-4.2 to 9.8) *(n=25)*	**2.3** (-2.2 to 6.8)	**3.0** (-5.3 to 11.3)	**2.1** (-1.9 to 6.1)

Table 5: Potential for Inappropriate Dose Changes from Predictive Equations

	Actual	1	2 *(n=30)*	3 *(n=30)*	4	5	6
< 4 µmol/L (n)	13	5	14	6	12	13	12
4 - 8 µmol/L (n)	16	23	11	15	23	22	23
> 8 µmol/L (n)	15	16	5	9	9	9	9
Potential for inappropriate change in dose (n,%)		11 (25)	14 (47)	6 (20)	11 (25)	12 (27)	11 (25)

Results

- The Winter-Tozer equation tended to overpredict
- The May et al., Kane et al. (Equations 4 & 5), Haidukewych et al., and Cheng et al. equations tended to underpredict

Limitations

- eGFR used instead of CrCl for Equation 5
- Free PHT assay at VGH changed Feb 27, 2012
  - 18 concentrations after this date, 26 concentrations before
- Small sample size
- Interacting medication not at steady state

Conclusions

- Overall predictive performance of currently developed equations poor
- In general, the Cheng et al. equation was the most precise; the Haidukewych et al. equation was the least biased
- Larger sample sizes required to derive new equations with reduced bias and/or increased precision

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Vancouver CoastalHealth Promoting wellness. Ensuring care.
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