CYP2D6: Nortriptyline

AUC: Area under the concentration-time curve, Clor: oral clearance, Css: steady state plasma concentrations, EM: extensive metabolizer, HNT: 10-hydroxynortriptyline, IM: intermediate metabolizer, MR: metabolic ratio, NS: not statistically significant, NT: nortriptyline, PM: poor metabolizer, S: statistically significant, t1/2: elimination half-life, UM: ultrarapid metabolizer.

Reference	Level of evidence	Clinical relevance	Effect	Remarks
ref. 1 Lee SY et al. Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit 2006;28:382 -7. PMID: 16778723	3	IM: A UM: AA	16 healthy Korean subjects, 12x EM (3x *1/*1, 8x *1/*10, 1x *2/*10), 3x IM (2x *10/*10, 1x *5/*10), 1x UM (*2N/*10). 15 mg NT single dose. Compared to EM: - IM: AUC NT increased from 743.2 to 1898.4 µg.hr/l (S, by 155%) - UM: AUC NT increased from 743.2 to 572.0 µg.hr/l (NS, by 23%)	AUC NT compared to EM: IM: 255% UM: 77%
ref. 2 Lee S et al. A case report of a poor metabolizer of CYP2D6 presented with unusual responses to nortriptyline medication. J Korean Med Sci 2004;19:750- 2. PMID: 15483356	2	IM: C	Patient (*5/*10) prescribed 150 mg/day NT developed adverse effects (dry mouth, constipation, and dizziness). C_{ss} was 471 µg/l. No adverse effects occurred after dose reduction to 50 mg/day.	
ref. 3 Roberts RL et al. No	3	PM: AA	60 patients, 56x EM (carriers of *1, *2, *9 or *10), 4x PM (*4/*4 or	Conclusion authors: 'These findings suggest that inability to

evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Hum Psychopharmacol. 2004;19:17-23. PMID: 14716707			*4/*5). 25-75 mg NT for 3 days. At that point dose was adjusted to clinical response, adverse effects and drug plasma levels. Study duration was 6 weeks, no relevant concomitant medication. Compared to EM: - PM: Comparable frequency of adverse effects after 6 weeks - Slightly lower NT dose after 6 weeks Note: measurement of ADE after 3 and 6 weeks could be biased because dose adjustments in response of ADE were allowed.	efficiently metabolize antidepressants that are CYP2D6 substrates does not necessarily lead to increased occurrence of antidepressant -associated adverse drug reactions.'
ref. 4 Dalen P et al. Disposition of debrisoquine and nortriptyline in Korean subjects in relation to CYP2D6 genotypes, and comparison with Caucasians. Br J Clin Pharmacol 2003;55:630-4. PMID: 12814461	3		10 healthy subjects, 5x *1/*1, 5x *1/*10. 25 mg NT single dose. No concomitant medication. Compared to *1/*1: - *1/*10: - AUC NT increased from 1591 to 1672 nM·hr (NS, by 5%). - Clor decreased from 1.9 to 1.0 l/kg/hr (NS, by 47%). - AUC HNT decreased from 2317 to 2143 (NS, 8%). - Ratio AUC NT/HNT increased from 0.69 to 0.77 (NS, 12%).	
ref. 5 Murphy GM et al. CYP2D6 genotyping with oligonucleotide microarrays and	3	IM: A	36 geriatric patients, 18x EM (5x *1/*1, 12x *1/*2, 1x *1/*10) and 16x IM (2x *1/*3, 4x *1/*4, 1x *5/*10, 3x *2/*10, 2x *2/*2, 4x *2/*4,1x *3/*4, 1x *4/*4). NT dosed	

nortriptyline concentrations in geriatric depression. Neuropsycho-pharmacol 2001;25:737 -43 PMID: 11682257			at target plasma concentration of 50-150 µg/l. Concomitant medications allowed. Compared to EM: - IM: Css^b NT increased from 1.3 to 2.9 ng/ml (S, by 123%). Prescribed dose was lower 66.9 vs 43.3 mg (S, by 30%) Note: effect of the concomitant medication on CYP2D6 activity is unclear.	Css NT IM compared to EM: 223%
ref. 6 Kvist EE et al. Quantitative pharmacogenetics of nortriptyline: a novel approach. Clin Pharmacokinet. 2001;40:869 -77. PMID: 11735606	3	PM: AA IM: AA UM: AA	20 patients and 20 healthy subjects. 5x no functional allele, 17x 1 functional allele, 12x 2 functional alleles, 6x ≥3 functional alleles (functional alleles: *1 and *2, non-functional alleles: *3, *4, *5). Patients received 50mg NT 3 times daily (1 subject 50mg twice daily). Healthy subjects received 25 or 50mg NT single dose. No concomitant medication. Compared to 2 functional alleles: no functional alleles: - Clor decreased from 65.5 to 25.1 l/h (NS, by 62%) 1 functional allele: - Clor decreased from 65.5 to 45.3 l/h (NS, by 31%) 3 functional alleles: - Clor increased from 65.5 to 85.7	Clor NT compared to EM: PM: 38% IM: 69% UM: 185%

			l/h (NS, by 31%) 4 functional alleles: - Clor increased from 65.5 to 105.9 l/h (NS, by 62%) 13 functional alleles: - Clor increased from 65.5 to 278.7 l/h (NS, by 325%) The number of functional CYP2D6 alleles explained 21% of the interindividual variance in Clor and 34% of the interindividual variance in NT Css Note: patients were genotyped but only the number of functional alleles was reported.	
ref. 7 Morita S et al. Steady-state plasma levels of nortriptyline and its hydroxylated metabolites in Japanese patients: impact of CYP2D6 genotype on the hydroxylation of nortriptyline. J Clin Psychopharmacol 2000;20:141 -9. PMID: 10770451	4	IM: A	41 patients, 7x *1/*1, 8x *1/*2, 16x *1/*10, 1x *2/*10, 3x *1/*5, 5x *10/*10, 1x *5/*10. NT 15-120 mg/day. No relevant concomitant medication. Compared to no mutation: 2 mutations (*10/*10, *10/*5): - Css^b NT increased from 70.3 to 147 ng/ml/mg/kg (S, by 109%), - Css^b HNT decreased from 89.6 to 59.8 ng/ml/mg/kg (S, by 33%). - Ratio NT/HNT increased from 0.82 to 2.71 (S, by 230%). 1 mutation (*1/*10, *2/*10, *1/*5): - Css^b NT increased from 70.3 to	Css^b NT compared to EM (*1/*1+* 1/*2+ *1/*10+ *2/*10+*1/*5): IM: 170%

			98.4 ng/ml/mg/kg (S, by 40%), - Css[b] HNT increased from 89.6 to 107 ng/ml/mg/kg (NS, by 19%). - Ratio NT/HNT increased from 0.82 to 1.04 (NS, by 27%).	
ref. 8 Yue QY et al. Pharmacokinetics of nortriptyline and its 10- hydroxy metabolite in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther 1998;64:384 -90. PMID: 9797795	3	IM: A	15 healthy subjects, 5x *1/*1, 5x *1/*10, 5x *10/*10. 25 mg NT single dose. No concomitant medication. Compared to *1/*1: *10/*10: - AUC NT increased from 1817 to 4002 nM·h (NS, by 120%), - Clor NT decreased from 1.86 to 0.80 l/h/kg (NS, by 57%). - AUC HNT decreased from 2273 to 1704 nM·h (S, by 25%). - Ratio AUC NT/HNT increased from 0.82 to 2.51 (by 244%). *1/*10 - AUC NT increased from 1817 to 2492 nM·h (NS, by 37%) - Clor NT decreased from 1.86 to 1.39 l/h/kg (NS, by 25%). - AUC HNT increased from 2273 to 2975 nM·h (NS, by 31%). - Ratio AUC NT/HNT increased from 0.82 to 0.94 (by 15%).	AUC NT compared to EM (*1/*1+*1/*10): IM: 186%
ref. 9 Dalen P et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional	3	PM: A IM: A UM: A	20 healthy subjects, 4x *4/*4, 5x *1/*1, 3x *1/*4, 2x *1/*5, 5x *2x2/*2, 1x *2x13/*1. 25 mg NT single dose (UM 50 mg). No concomitant medication.	AUC NT compared to EM: PM: 332% IM: 279%

CYP2D6 genes. Clin Pharmacol Ther 1998;63:444 -52. PMID: 9585799			Compared to EM: 0 functional alleles: - AUC NT increased from 1295 to 4301 nM·hr (S, by 232%) - t1⁄2 NT is 54.5 hr. - AUC HNT decreased from 1711 to 1537 nM·hr (NS, by 10%) - t1⁄2 HNT is 52.2 hr. - Ratio AUC NT/HNT increased from 0.77 to 2.89 (S, by 275%). 1 functional allele: - AUC NT increased from 1295 to 3617 nM·hr (S, by 179%) - t1⁄2 NT is 47.5 hr - AUC HNT increased from 1711 to 1856 nM·hr (NS, by 8%) - t1⁄2 HNT is 39.7 hr. Ratio AUC NT/HNT increased from 0.77 to 2.06 (S, by 168%). 3 functional alleles: - AUC NT decreased from 1295 to 860 nM·hr (NS, by 34%), - t1⁄2 NT is 18.1 hr. - AUC HNT increased from 1711 to 2731 nM·hr (NS, by 60%) - t1⁄2 HNT is 17.6 hr. - Ratio AUC NT/HNT decreased from 0.77 to 0.32 (S, by 58%). 13 functional alleles: - AUC NT decreased from 1295 to 267 nM·hr (NS, by 79%) - t1⁄2 NT is 19 hr. - AUC HNT increased from 1711	UM: 59%

			to 3442 nM·hr (NS, by 101%) - t1⁄2 HNT is 9.5 hr. - Ratio AUC NT/HNT decreased from 0.77 to 0.08 (NS, by 90%).	
ref. 10 Dahl M et al. Steady-state plasma levels of nortriptyline and its 10-hydroxy metabolite: relationship to the CYP2D6 genotype. Psychopharmacol 1996;123:315-9. PMID: 8867869	3	PM: A IM: A	21 patients, 7x *1/*1, 13x *1/*3 of *1/*4 of *1/*5, 1x *4/*4. 150 mg NT/day (1 patient 100 mg/day). Concomitant medication unknown. Compared to *1/*1: PM: - Css NT increased from 2.60 to 6.40 (S, by 146%) - Css HNT decreased from 5.20 to 4.50 (S, by 13%) - Ratio Css NT/HNT increased from 0.5 to 1.4 (S, by 180%). IM (*1/*3, *1/*4, *1/*5): - Css NT increased from 2.60 to 3.50 (NS, by 35%) - Css HNT decreased from 5.20 to 3.50 (S, by 33%) - Ratio Css NT/HNT increased from 0.5 to 1.0 (S, by 100%).	Css NTcompared to EM: PM: 246% IM: 135%
ref. 11 Chen S et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry.	1	IM: C PM: C	8 patients (4x *1/*1, 1x *1/*3, 1x *1/*4, 1x *3/*9, 1x *4/*4) experienced adverse effects after NT 10-75 mg/day. Concomitant medication unknown. Reported NT related adverse effects by IM and PM: - *1/*3: 25-50 mg/day: nervousness, tinnitus	

Clin Pharmacol Ther 1996; 60:522 -34 PMID: 8941025			- *1/*4: 75-100 mg/day: Unsteadiness (shaking in knees), nervousness - *3/*9: 10 mg/day: sleepiness, sluggishness -*4/*4: 10 mg/day: increased anxiety, agitation, nervousness Note: there is no analysis if reported adverse effects might be disease related	
ref. 12 Bertilsson L et al. Molecular basis for rational megaprescribing in ultrarapid hydroxylators of debrisoquine. Lancet 1993;341:63. PMID: 8093319	2	UM: C	Patient (UM) required NT dose increase up to 500 mg/day (3-5 times the recommended dose) to attain therapeutic plasma levels.	
ref. 13 Bertilsson L et al. Slow hydroxylation of nortriptyline and concomitant poor debrisoquine hydroxylation: clinical implications. Lancet 1981;1:560-1. PMID: 6111662	2	PM: C	Patient complained of dizziness and hypotension 2 days after the start of NT 75 mg/day. After a further 6 days of treatment he complained of increasing tiredness and vertigo and appeared slightly confused. Css was 1300 nmol/l (usual range on this dosage 200-600 nmol/l). After 12 days of NT 25 mg/day Css dropped to 742 nmol/l. Adverse effects disappeared after a further dose reduction to 20 mg/day	

[a] adjusted for dose

[b] adjusted for dose and bodyweight
#: Calculations assumed the potency of 10-hydroxynortriptyline to be 50% of that of nortriptyline

Groups at risk	IMs prescribed a CYP2D6 inhibitor

Remarks
Date literature search: 10 January 2008

	Phenotype	Code	Gene-Drug Interaction	Action Required	Date
Decision DPWG	PM	3 C	Yes	Yes	26 March 2008
	IM	4 C	Yes	Yes	
	UM	3 C	Yes	Yes	

Action Pharmacy Technician	First prescription: Consult pharmacist Subsequent prescription: Dispense. If genotype was not previously known, consult pharmacist.
Action Pharmacist, Physician	PM: Reduce dose to 40% of the recommended dose and titrate dose in response of nortriptyline + 10-hydroxynortriptyline plasma concentrations
	IM: Reduce dose to 60% of the recommended dose and titrate dose in response of nortriptyline + 10-hydroxynortriptyline plasma concentrations
	UM: Select alternative drug (e.g. citalopram, sertraline). If this is not possible increase dose to 160% of the recommend dose and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations. There are reports that E-10-hydroxynortriptyline is cardiotoxic.

Considerations
Dose adjustments were calculated from nortriptyline AUC or Css data.
PM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 35% of the recommended dose (30% - 41%). For clinical applicability this is translated to a reduction to 40% of the recommended dose. Monitor plasma concentrations after dose adjustment.

IM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 58% of the recommended dose (36% - 74%). For clinical applicability this is translated to a reduction to 60% of the recommended dose. Monitor plasma concentrations after dose adjustment.

UM: The population size-weighted mean of the dose adjustments calculated for the individual papers is 174% of the recommended dose (130% - 185%). For clinical applicability this is translated to an increase to 160% of the recommended dose. However, since it is difficult to find the right nortriptyline dose in UMs (Ther Drug Monit 1985;7:478-80), it is advised to select a drug that is not metabolized by CYP2D6. Only if this is not possible a dose increase should be considered.

Dose calculations were not adjusted for the 10-hydroxynortriptyline concentrations. Adjusting for E-10-hydroxynortriptyline concentrations would have resulted in smaller dose adjustments.

Mechanism

Nortriptyline is metabolized by CYP2D6 to the active metabolite E-10-hydroxynortriptyline. The potency of E-10-hydroxynortriptyline is approximately 50% lower compared to the parent drug. A genetic polymorphism in CYP2D6 results in altered concentrations of nortiptyline and E-10-hydroxynortriptyline. Nortriptyline is metabolized to the inactive desmethyl metabolite by CYP2D6 and CYP2C19.