# Amitriptyline reconsidered

## *The relevance of dosage regimen, serum concentrations, genotypic measures and adverse outcomes*

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## PURPOSE

Tricyclic antidepressants have played leading roles in psychiatric pharmacotherapy, with amitriptyline credited in the management of depression, and later also in neuropathic pain. It is accepted clinical practice to initiate therapy at a low dose, adjusting gradually to support tolerability. Exposure to amitriptyline and its metabolites is influenced by genetic polymorphisms of the cytochrome P450 subfamily enzymes[1], particularly CYP2C19 and CYP2D6. Evaluating the interplay between adverse outcomes and serum concentrations, as may be moderated by the dosage regimen and genotype-inferred variability on individual pharmacokinetics, should enable better informed use of this established drug (Figure 1).

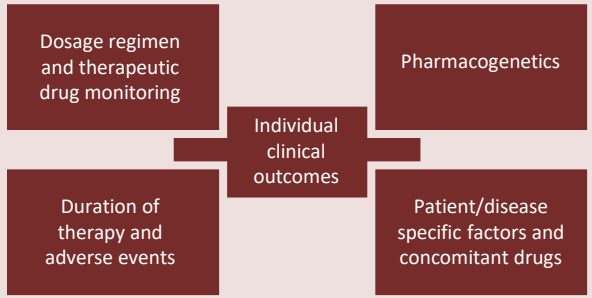


**Figure 1:** Interplay between potential confounding factors, for consideration in delivering precision pharmacotherapy

## METHODS

Following written informed consent, 44 out-patients on amitriptyline therapy (32 females and 12 males), were recruited from Mater Dei Hospital, Malta. The amitriptyline dose administered in the subjects ranged between 10mg and 175mg per day. Blood was withdrawn 11-18 hours post-dose from all patients in steady-state, and any co-administration of CYP inhibitors was recorded. LC-MS/MS was used to determine serum concentrations of amitriptyline, its active metabolite nortriptyline, and the hydroxy-metabolites. Buccal swabs were collected to determine CYP2C19 and CYP2D6 genotype and metabolizer phenotype. Two patients were excluded due to inconclusive laboratory results.

Patients reported the total side effect burden associated with amitriptyline and scored the 21 items indexed in the Antidepressant Side Effect Checklist (ASEC)[2] on a four-point scale (0 absent; 1 mild; 2 moderate; 3 severe). The two most reported side effects, drowsiness and dry mouth, were selected for further study. A time parameter was added in investigating these adverse outcomes, categorising patients into: having been administered amitriptyline for (i) less than 12 months, or (ii) over 12 months.

## RESULTS

All measured serum concentrations positively correlated to the daily amitriptyline dose ($P<0.01$). Total side-effect burden did not correlate to concentrations. CYP2C19 and CYP2D6 genotypic measures and risk of CYP inhibition by concomitant drugs, did not render significant correlations to total side-effect burden and neither to dry mouth nor drowsiness scores. Dry mouth score positively correlated to the concentrations of amitriptyline, nortriptyline, amitriptyline + nortriptyline, and Z-10-hydroxynortriptyline. From patients with less than 12 months therapy, 17% reported dry mouth, compared to 53% of patients with over 12 months therapy who reported dry mouth and had higher severity scores, corresponding to their higher amitriptyline doses and concentrations. Drowsiness unexpectedly showed a negative correlation to the concentrations of nortriptyline, amitriptyline + nortriptyline, and Z-10-hydroxynortriptyline. These correlations were significant at the 0.05 level. Incidence and severity score of drowsiness were higher in patients on amitriptyline for less than 12 months, whose daily dose and concentrations were significantly lower ($P<0.01$). The parsimonious linear regression models indicate that patients with less than 12 months therapy are 11 times more likely to report drowsiness and 6 times less likely to report dry mouth compared to patients with over 12 months therapy.

## CONCLUSIONS

The reported outcomes infer that drowsiness may become less problematic in the long-term, even upon dose escalation, while dry mouth may persist over months of amitriptyline use and is perceived to interfere sufficiently in patient quality of life to merit reporting. These observations may challenge the general notion of tolerance to anticholinergic adverse effects, suggesting that tolerance may not necessarily develop, with anticholinergic side effects possibly fluctuating in their occurrence. The study demonstrates the implications of precision medicine for established drugs like amitriptyline as a complement to the evaluation of confounding factors which impact individual clinical outcomes.

### References

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2. Uher R, Farmer A, Henigsberg N, Rietschel M, Mors O, Maier W et al. Adverse reactions to antidepressants. *Br J Psychiatry* 2009;195(3):202-10.

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