Illustration of the combined effect of patient’s adherence and individual biological characteristics on blood pressure.

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Introduction: About Drug forgiveness

The problem:
What is the protective effect of a drug against non-adherence?

The answer:
Forgiveness is an evidence-based parameter that defines how long a drug’s therapeutically effective action continues after a last-taken dose, and can thus continue to provide therapeutic action(s) in the face of occasional dosing lapses of varying durations.

Drawbacks of the usual approach

- Forgiveness typically reported as a group average value, ignoring person-to-person variability.
- Ignores more complex patterns of non-adherence such as delays in intakes, missed doses, week-end effect, drug holidays … their recurrence and combination.

Proposed approach:
Alternative way of estimating and presenting information on drug forgiveness which allows estimation of the combined effect of imperfect adherence and variable forgiveness.
Simulations acknowledging for two important sources of variability in drug response.

**Step 1**
- **ADHERENCE**

**Step 2**
- **BIOLOGY**
- **PK/PD CHARACTERISTICS**

**Step 3**
- **BEHAVIOUR**
- **INDIVIDUAL DRUG RESPONSE**

**Step 4**
- **INDIVIDUAL MEASURE OF FORGIVENESS**

**Step 5**
- **PROTECTIVE EFFECT AGAINST NON-ADHERENCE**

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Step 1: Adherence data

Projected dosing histories over 365 days were obtained from 4783 patients with hypertension.

1. Daily probability of intake
2. Distribution of intake times

Observed adherence data

Projected Adherence data
Step 2: Effect of drug cessation on SBP

A dataset of systolic blood pressures (SBP) was obtained by pooling data recorded during the treatment with an anti-hypertensive drug and after its cessation.

Baseline mean sitting SBP
Mean sitting SBP at withdrawal visit
Mean sitting SBP post-withdrawal
Step 2: Effect of drug cessation on SBP

Longitudinal SBP collected from 4879 patients after drug withdrawal were analysed using non-linear mixed effect models based on an exponential decay function, allowing the estimation of the between-patient variability in the loss of effect.

Mixed Model description

Mixed Model predictions

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Combining adherence and SBP Data (principle)

Assume steady state

Simulated individual adherence profile

+ Sampled individual off-parameters (int, delta, rate)

on-slope = delta/14 days

rate

delta

Intercept

= Individual Projected SBP profile
Step 3: Projected SBP curves

Frequent missed doses and drug holidays

Intravenous infusion

Patient 18 (Execution 46.9 %)

Days

0 5 10 15 20 25

0 50 100 150 200 250 300 350

Day of intake

Irregular intakes and missed doses

Patient 380 (Execution 75.9 %)

Days

0 5 10 15 20 25

0 50 100 150 200 250 300 350

Day of intake

Frequent drug holidays

Patient 2377 (Execution 84.9 %)

Days

0 5 10 15 20 25

0 50 100 150 200 250 300 350

Day of intake

Frequent missed doses and drug holidays

Patient 22 (Execution 60 %)

Days

0 5 10 15 20 25

0 50 100 150 200 250 300 350

Day of intake
Step 4: Deriving Individual summary

Some individuals are more susceptible to significant losses of effect than others. A 3 mmHg increase in SBP is clinically relevant and constitutes a break in the continuity of drug action.

For each individual SBP trajectory, we estimate the number of days with a loss of at least 3 mmHg over a 365 treatment period.
Step 5: Estimating the protective effect against non-adherence

Results

In this population of hypertensive patients, 90% of the patients maintained the maximal effect during 95% of the time.
Step 5: Estimating the protective effect against non-adherence

Sensitivity

Distribution of execution

Assuming a lower adherence, about 80% of the patients maintained the maximal effect during 95% of the time
Conclusion

The impact imperfect adherence on response is mitigated by forgiveness.

This methodology

✓ reveals the person-to-person variability in clinical effectiveness which is hidden when forgiveness is considered as a group-average quantity

✓ shows that the agent studied provides a reliable clinical effectiveness despite imperfect adherence.

Beyond the state-of-the-art

Ultimately, this approach could be used to compare drugs with different levels of forgiveness and/or regimens in the presence of non-adherence.