6th YSS (in collaboration with with the Universities of Bologna (It.) and Ghent (B.))

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Future-proofing Bioanalysis - Contributing to a sustainable world

The meeting will be organised simultaneously in
different regions on 24 and 25 September 2020 combined with a live streaming

Novel microfluidic-based sampling for therapeutic drug monitoring of patients under treatment with the antidepressant drug vortioxetine

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DEPRESSIVE DISORDERS: A COMPLICATED SCENARIO

Depression is one of the leading causes of disability worldwide

affects people of all ages, more women than men

may begin with mood fluctuations and become a serious health condition that can lead to suicide

complex interaction of social, psychological and biological factors

wide-ranging and growing phenomenon affecting the physical and psychic sphere of patients

Types of Depression:

- major depressive disorder (MDD)
- persistent depressive disorder (dysthymia)
- manic depression, postpartum depression, atypical depression, premenstrual dysphoric disorder…

→ **psychological treatment**

→ **antidepressant medication**

World Health Organization Media Centre, "Depression". http://www.who.int/mediacentre/factsheets/fs369/en/

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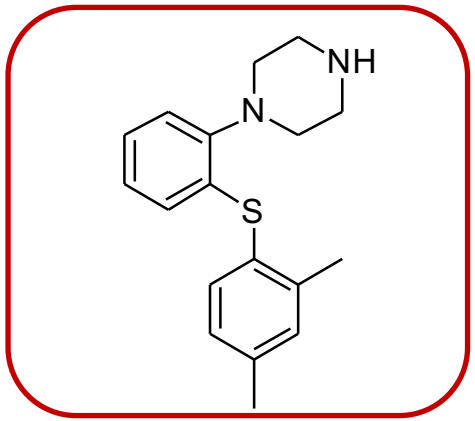
ANTIDEPRESSANT MEDICATION

- "First generation" → Tricyclic Antidepressants (TCA), Monoamine Oxidase Inhibitors (MAOI)
- "Second-generation" or "new-generation" antidepressants (NGA) → Selective Serotonin Reuptake Inhibitors (SSRI)
- "non-SSRI" → **Serotonin Modulator and Stimulator (SMS)**, SNRI, SARI, NaSSA, NeRI, SNDRI, TRI, MaSA



Vortioxetine

- belongs to SMS class
- approved in both the USA and the EU in 2013 exclusively for the treatment of MDD
- extensive hepatic metabolism, but metabolites are not pharmacologically active
- common side effects include diarrhea, nausea, vomiting…

R. Mandrioli, M. Protti, L. Mercolini.
Current Medicinal Chemistry 25 (2018) 772-792.

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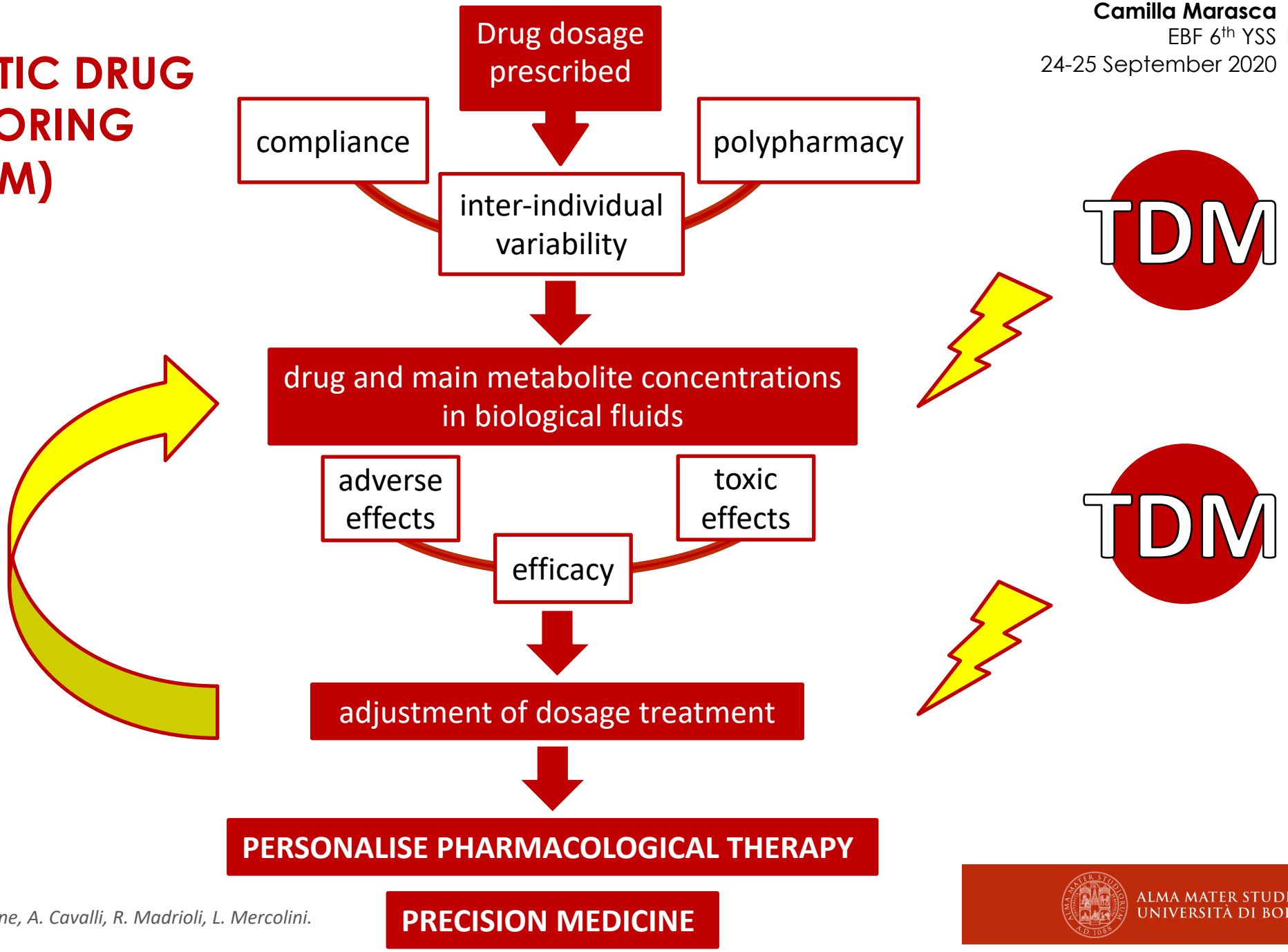
THERAPEUTIC DRUG MONITORING (TDM)



M. Protti, C. Marasca, M. Cirrincione, A. Cavalli, R. Madrioli, L. Mercolini. Analyst 145 (2020) 5744-5753.

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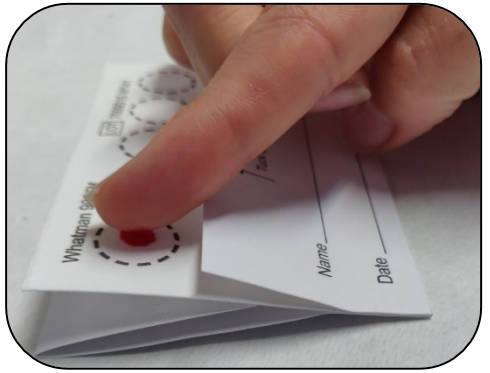
MICROSAMPLING

In-tube wet samples

wet microsampling



dry microsampling

- sample volume > 200 mL
- qualified personal
- invasive blood collection
- cryopreservation

- sample volume < 50 µL
- minimally invasive capillary blood collection
- storage and transport at RT
  → analyte stability
- no centrifugation
- no biological risk

C. Marasca, M. Protti, R. Mandrioli, A.R. Atti, A. Armirotti, A. Cavalli, D. De Ronchi, L. Mercolini. Journal of Pharmaceutical and Biomedical Analysis 188 (2020) 113384.

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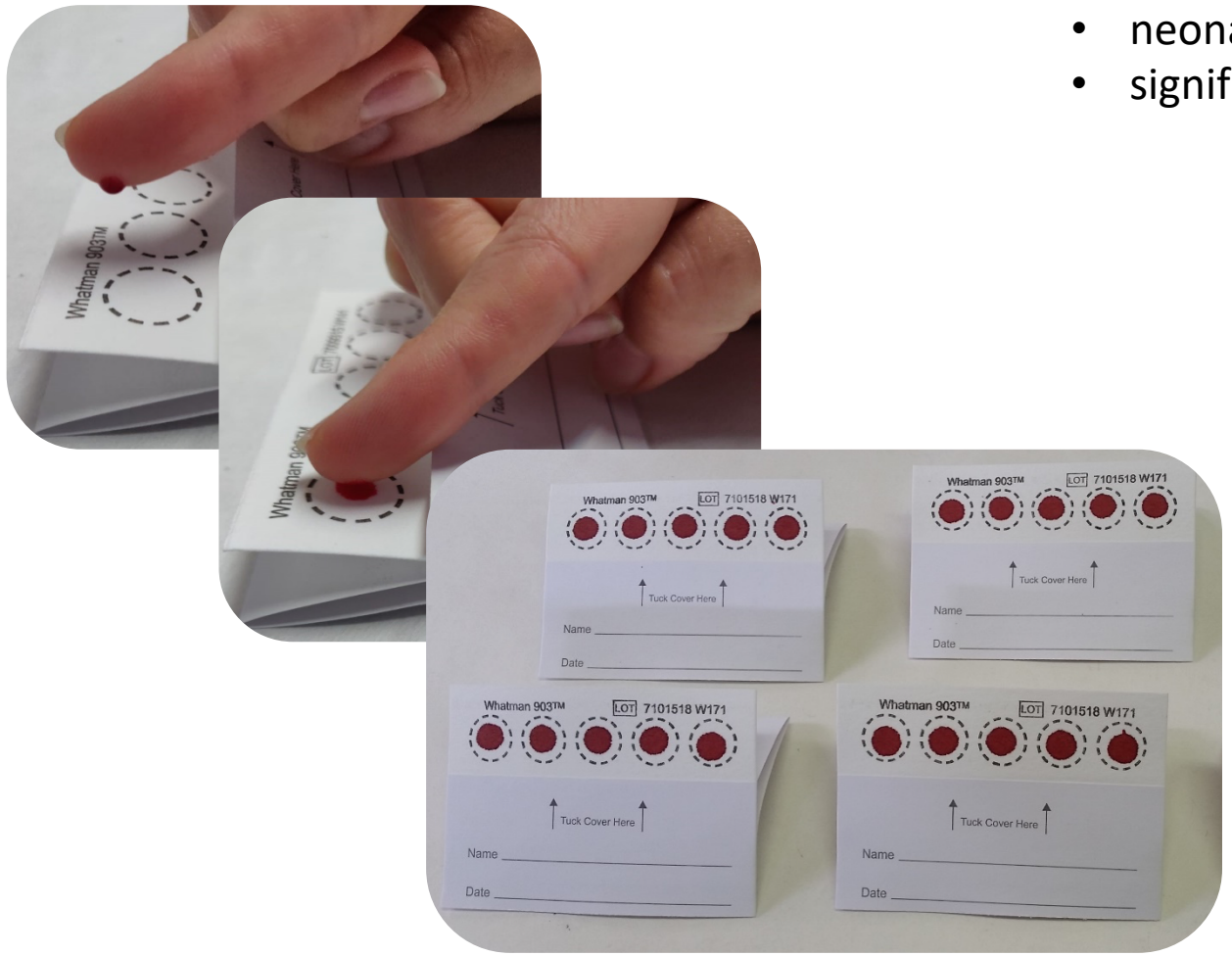
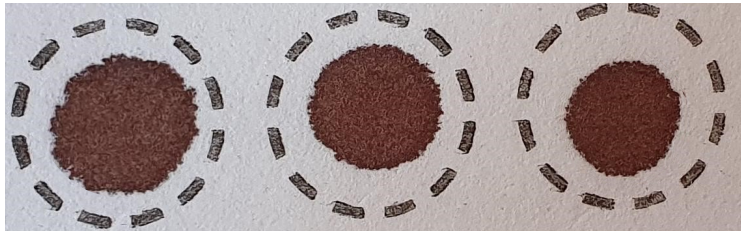
FROM DRIED BLOOD SPOT (DBS)…



- neonatal screening for 50+ years
- significant advantages in terms of collection and processing

HAEMATOCRIT ISSUE

HCT 20 % **HCT 45 %** **HCT 70 %**



→ volumetric bias,
reflecting on spot size and homogeneity,
sampling reproducibility,
accuracy and precision of analytical data

→ For quantitative analysis, an accurate volume needs to be spotted or punched from the sample

M. Protti, R. Mandrioli, L. Mercolini.
Analytica Chimica Acta 10476 (2019) 32-47.

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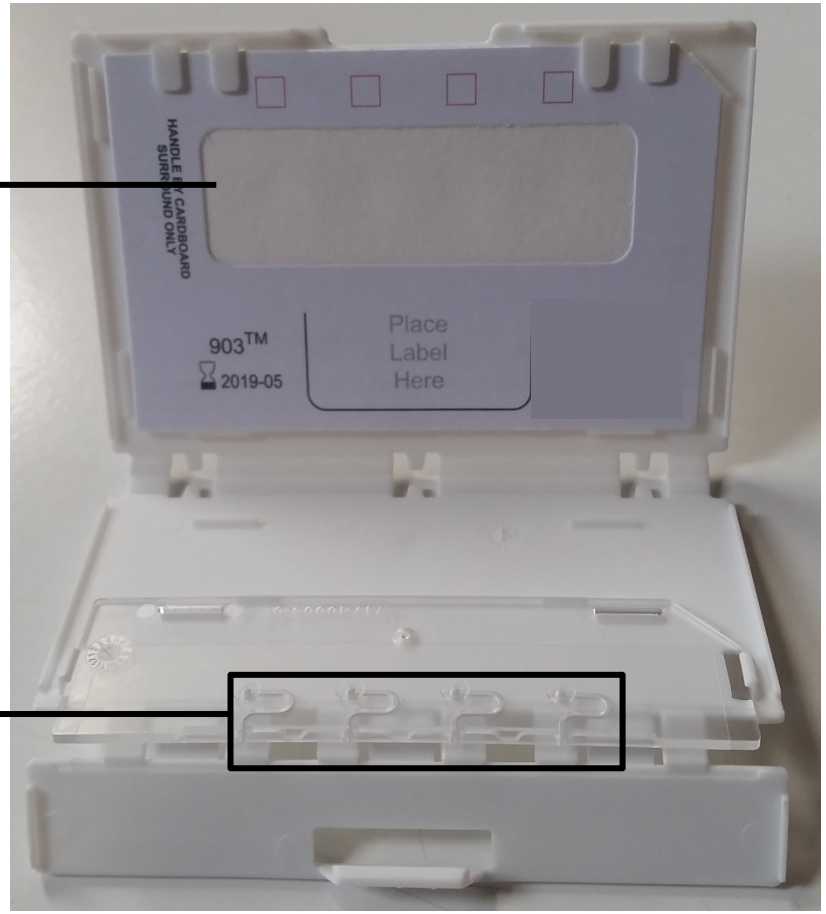
…TO MICROFLUIDIC CHANNEL-BASED TECHNOLOGY

Filter card panel

Microfluidic channels



- Collection of 10 µL of capillary whole blood from fingerprick
- Once the channel is completely filled, the closure of the device generates 10-µL fixed-volume DBS
- Consecutive collection of 4 DBS samples on a single device

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AIM OF THE RESEARCH WORK

Design, development and optimisation of microsampling approach based on innovative microfluidic technology coupled to original LC-DAD-MS/MS method for vortioxetine analysis

- Extraction procedure
- MS/MS conditions

Validation studies

- Extraction yield
- Precision
- Calibration
- HCT assays
- Matrix effect
- Carry over
- Selectivity
- Accuracy

Application for TDM of patients with depressive disordes undergoing vortioxetine therapy

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PRETREATMENT & LC-MS/MS SYSTEM

Extraction procedure

- 10 µL DBS extraction
  and
- Injection in LC-MS system

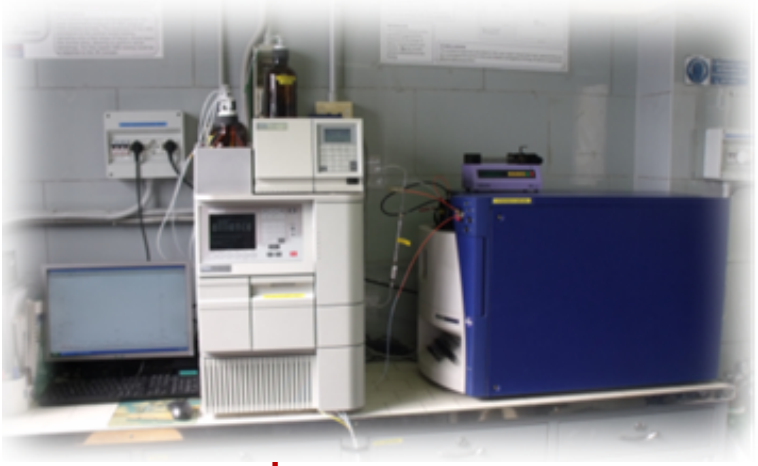
Straightforward procedure

Fast and feasible analysis

LC-MS/MS system

Analyser: Triple quadrupole (MS/MS)

Acquisition: MRM



VALIDATION RESULTS

Selectivity (n=6)	✓
Extraction yield (n=3)	✓
Matrix effect (n=3)	✓
Carryover (n=3)	✓
Calibration (5 conc., n=3)	✓
Precision (n=6)	✓
Accuracy (n=3)	✓

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MICROSAMPLING APPROACH APPLICATION

→ Collection of 10 µL DBS of capillary blood from patients with depressive disordes under vortioxetine therapy by means of microfluidic device

→ The optimised methodology was applied for TMD purposes in order to evaluate drug concentration in microfluidic-generated DBS

→ The quantitative results of the novel microfluidic approach were compared with those of reference plasma analysis

CONCLUSION

- An original miniaturised strategy based on innovative microfluidic technology, fast pretreatment and a sensitive LC-MS/MS method was developed for the analysis of the antidepressant vortioxetine
- An HCT study was carried out to demonstrate the independence of blood collection with microfluidic device from blood density
- The optimised methodology was applied to real samples for TDM of patients with depressive disorders undergoing vortioxetine treatment
- The results obtained from microsampling approach were compared with those of reference plasma procedure showing good agreement

- The microfluidic channel-based platform proved to be suitable for TDM purposes and represents a promising tool for the implementation in clinical practice thanks to the significant advantages in terms of patient compliance, sample handling and processing in order to perform a more frequent TDM reaching a personalisation of pharmacological therapy in the perspective of precision medicine

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