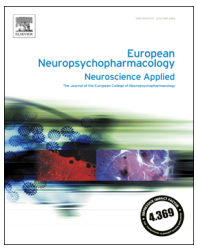
European Neuropsychopharmacology (2017) **27**, 205–216

www.elsevier.com/locate/euroneuro



REVIEW

Dried Blood Spot sampling in psychiatry: Perspectives for improving therapeutic drug monitoring

Lisa C. Martial[a,b], Rob E. Aarnoutse[a,b], Martina Mulder[c], Arnt Schellekens[c,d,e], Roger J.M. Brüggemann[a,b], David M. Burger[a,b], Aart H. Schene[c,d], Albert Batalla[c,e,*]

[a]*Radboud University Medical Center, Department of Pharmacy, Nijmegen, The Netherlands*
[b]*Radboud Institute for Health Sciences, Nijmegen, The Netherlands*
[c]*Radboud University Medical Center, Department of Psychiatry, Reinier Postlaan 10, Route 966, 6500 HB Nijmegen, The Netherlands*
[d]*Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen, Nijmegen, The Netherlands*
[e]*Radboud University, Nijmegen Institute for Scientist-Practitioners in Addiction, Nijmegen, The Netherlands*

Received 8 August 2016; received in revised form 2 December 2016; accepted 5 January 2017

KEYWORDS
TDM;
Dried blood spot;
Finger prick;
Antipsychotics;
Mood stabilizers;
Antidepressants

Abstract
Assessment of drug concentrations is indicated to guide dosing of a selected number of drugs used in psychiatry. Conventionally this is done by vena puncture. Novel sampling strategies such as dried blood spot (DBS) sampling have been developed for various drugs, including antipsychotics, antidepressants and mood-stabilizers. DBS sampling is typically performed by means of a finger prick. This method allows for remote sampling, which means that patients are not required to travel to a health care facility. The number of DBS assays for drugs used in psychiatry has increased over the last decade and includes antidepressants (tricyclic and serotonin and/or norepinephrine reuptake inhibitors), mood stabilizers and first- and second-generation antipsychotics. Available assays often comply with analytical validation criteria but are seldom used in routine clinical care. Little attention has been paid to the clinical validation

*Corresponding author at: Radboud University Medical Center, Department of Psychiatry, Reinier Postlaan 10, Route 966, 6500 HB Nijmegen, The Netherlands. Fax: +31 243 610 304.
E-mail address: abatallacases@gmail.com (A. Batalla).

http://dx.doi.org/10.1016/j.euroneuro.2017.01.009

and implementation processes of home sampling. Ideally, not only medicines but also clinical chemistry parameters should be measured within the same sample. This article reflects on the position of DBS remote sampling in psychiatry and provides insight in the requisites of making such a sampling tool successful.

1. Introduction

Monitoring of plasma drug concentrations and clinical chemistry tests is an important component of modern personalized pharmacological therapy in psychiatry. Traditionally, plasma or serum are used for these analyses, as these matrices are easy to handle and stable upon storage. Repeated sampling can be challenging, however, as venous sampling can only be performed in equipped health-care facilities and as such poses a burden for the patient. Dried blood spot (DBS) sampling provides an elegant alternative. It was first introduced more than fifty years ago as a sampling method in newborn screening 'heelprick' for phenylketonuria (Newman and Starr, 1971). A DBS sample can be obtained by means of a finger prick by spotting a drop of blood directly onto filter paper. The sample can be taken by patients themselves at home and can be sent to the laboratory using regular post mail.

Over the past decade, there has been an increase in the development of bioanalytical assays to measure samples collected by means of DBS sampling (Stove and Spooner, 2015). Currently, its use has expanded to a wide range of purposes such as for preclinical and clinical research, large epidemiologic studies, HIV or Hepatitis C screening or analysis of laboratory tests (e.g. Vitamin D) (Chang et al., 2015; Hoeller et al., 2015; Soulier et al., 2016). However, despite the fact that novel strategies for (remote) monitoring are warranted in psychiatry (e.g. in order to improve medication compliance) (Millan et al., 2015) the potential applicability of DBS in this field remains largely unexplored.

One of the most promising clinical applications of DBS is for therapeutic drug monitoring (TDM). TDM allows individualizing of drug doses, guided by measurement of plasma drug concentrations. The aim is to keep a patient's plasma concentrations within a therapeutic range (Aarnoutse et al., 2003; Bruggemann and Aarnoutse, 2015; Lempers et al., 2015). Several criteria can be identified that are required in order for TDM to be useful. First, the patient's response cannot be assessed by clinical observations or predicted by the administered dose. Second, there exists a large inter-individual variation in pharmacokinetic parameters. Third, the relationship between the drug concentration and the pharmacological effect (or toxicity) must be known. Fourth, there is a narrow range of concentrations that are effective and well tolerated. Fifth, a validated laboratory assay must be available with a fast turn around time (Aarnoutse et al., 2003). Especially in case of long-term treatment in outpatient settings, DBS can be a very useful tool for TDM, providing a novel methodology that might help clinicians obtaining adequate responses, preventing concentration-related adverse events, monitoring interactions and improving treatment compliance.

Excellent candidate drugs for TDM are immunosuppressants, antimicrobial drugs (HIV, HepC and antifungal drugs) and antiepileptics but also some antidepressants, antipsychotics and mood stabilizers as they are used for long periods in outpatient settings, display wide inter-patient variability in their pharmacokinetics, have small therapeutic windows and require repetitive concentration measurements (Barraclough et al., 2011; Bruggemann and Aarnoutse, 2015; Martial et al., 2016; Wilhelm et al., 2014). In psychiatry, TDM is routinely indicated for a selection of drugs, including tricyclic antidepressants (TCAs), mood stabilizers (lithium, valproic acid, carbamazepine) and clozapine (Hiemke, 2016).

Despite the fact that DBS sampling has gained more attention over the past years and that it has a clear potential for application in routine clinical care, this sampling method still plays a marginal role in today's clinical practice in psychiatry. The aim of this manuscript is to describe the current progress of DBS in psychiatry, to discuss the benefits and drawbacks of this sampling method and to gain insight in the future potential applications of DBS in monitoring psychiatric treatment. To this end, we performed a review of the literature on (1) DBS assays measuring drug concentrations, (2) their clinical validation and (3) implementation studies for drugs commonly used in psychiatry. In addition, we provide a broader view of DBS in the context of TDM for psychiatric drugs and discuss the steps that are required in order to make DBS successful in this field of medicine.

2. Experimental procedures

2.1. Search strategy

The electronic search was performed using PubMed. A combination of the following terms was used: "dried blood spot" [All Fields] AND "psychiatry" [MeSH Terms], "antipsychotic" [All Fields], "antidepressant" [All Fields], "mood stabilizer" [All Fields], "antiepileptic" [All Fields]; "DBS (not deep brain stimulation)" [All Fields] AND "psychiatry" [MeSH Terms], "antipsychotic" [All Fields], "antidepressant" [All Fields], "mood stabilizer" [All Fields], "antiepileptic" [All Fields]. All studies published in any language up to April 2016 and indexed in the mentioned database were considered. The data was extracted by two reviewers (LM and AB). In addition, as to gather a broader view of DBS sampling and place this in the context of psychiatric treatment, we searched the literature for general review articles on DBS and pharmacological therapy.

2.2. Inclusion and exclusion criteria

Included were DBS studies involving antipsychotics, antidepressants, mood stabilizers and antiepileptic drugs: (1) investigating an analytical method to measure drug concentrations, (2) clinical validation studies and (3) implementation studies. Excluded were