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Review

Analytical methods for the quantitative determination of selective serotonin reuptake inhibitors for therapeutic drug monitoring purposes in patients

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Abstract

Five selective serotonin reuptake inhibitors (SSRIs) have been introduced recently: citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Although no therapeutic window has been defined for SSRIs, in contrast to tricyclic antidepressants, analytical methods for therapeutic drug monitoring of SSRIs are useful in several instances. SSRIs differ widely in their chemical structure and in their metabolism. The fact that some of them have N-demethylated metabolites, which are also SSRIs, requires that methods be available which allow therapeutic drug monitoring of the parent compounds and of these active metabolites. Most procedures are based on prepurification of the SSRIs by liquid–liquid extraction before they are submitted to separation by chromatographic procedures (high-performance liquid chromatography, gas chromatography, thin layer chromatography) and detection by various detectors (UV, fluorescence, electrochemical detector, nitrogen–phosphorus detector, mass spectrometry). This literature review shows that most methods allow quantitative determination of SSRIs in plasma, in the lower ng/ml range, and that they are, therefore, suitable for therapeutic drug monitoring purposes of this category of drugs.

Keywords: Serotonin; Citalopram; Fluoxetine; Fluvoxamine; Paroxetine; Sertraline

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1. Introduction

The life-time prevalence of depression in the general population has been found to vary between 4.4–19.5%, depending on the study in which this question has been examined. In the Zurich study, about half of the subjects with a major depressive disorder or a brief recurrent depression needed treatment [1]. Recent research has shown that many patients suffer from recurrent depression which requires treatment for several years [2,3]. For pharmacotherapy of depression, tricyclic antidepressants (TCA) were introduced 40 years ago. Despite there being a long debate on the clinical usefulness of therapeutic plasma level monitoring (TDM) of these drugs, it is now widely accepted [4–6]. As it is, some TCA's optimal plasma level ranges have already been defined. Moreover, TCA are known to be relatively toxic drugs and, with increasing plasma levels, the risk of adverse effects increases sharply [7]. Furthermore, there are many patients who are non-compliant and the percentage of such patients increases with treatment duration. TDM may help to optimize pharmacological treatment and is also recommended in situations where the patients belong to special populations, such as elderly subjects or patients suffering from organic diseases which necessitate careful adaption of the treatment.

Over the past 10 years a group of five antidepressants have been introduced which differ from the TCA both in their chemical structure (Fig. 1) and in their mechanism of action. The selective serotonin reuptake inhibitors (SSRI), in contrast to TCA, do not significantly inhibit reuptake of norepinephrine in the nerve endings in vitro or in vivo. Moreover, they are mostly devoid of anticholinergic and antiadrenergic properties [8]. SSRI are comparable to TCA in their clinical efficacy but, due to their favourable pharmacological profile, they are considered to be safe and well tolerated drugs [9,10]. These properties as well as the fact that plasma level ranges, within which clinical response with minimal side effects appears to be optimal [5,6,11–15], are not clearly defined, may explain why TDM of these compounds has been little introduced. However, measuring SSRI concentrations may be useful at least for checking compliance, in case the patient does not respond to an apparently adequate dose and for such problems as drug interactions, pharmacokinetic studies, toxic manifestation, or administration of SSRI to special populations (i.e. elderly persons or people with organic diseases). Compliance is important, as it has been shown that up to 32% of patients in general practice stopped medication within six weeks after the beginning of the treatment, and 63% of these did not inform their general practitioners of their decision [16]. SSRIs showed only a slight, but non-significant, compliance advantage over TCAs in this study. Taking into account this high proportion of non-compliant patients, it is our opinion that the financial and social cost of a non-treated depressive episode largely outweighs the cost of TDM of SSRIs.

The five SSRIs presently available are citalopram (CIT), fluoxetine (FLX), fluvoxamine (FLV), paroxetine (PAR) and sertraline (SER). Some of them have also been introduced for other indications, such as obsessive compulsive disorders, bulimia and panic attacks, and their usefulness in some forms of alcoholism is also discussed. The SSRIs differ widely in their chemical structure (Fig. 1). This explains differences in their metabolism and pharmacokinetics [15,17,18].

2. Metabolism and pharmacokinetics of SSRIs

With regard to their analysis and to TDM, the following points are of particular relevance: FLV [11] is a primary amine and an achiral drug, for which no active metabolites are known. PAR [19] and SER [20,21] are secondary amines and both have two asymmetric centers, but for each compound only a single enantiomer has been introduced as an antidepressant. PAR is considered to have no active metabolite, in contrast to norsertraline (NSER), which is formed by N-demethylation and which is also an SSRI. FLX and CIT, a secondary and a tertiary amine, respectively, have been introduced as racemic drugs. FLX is demethylated to norfluoxetine (NFLX), and CIT to demethylcitalopram (DCIT) and didemethycitalopram (DDCIT). All these metabolites are SSRIs, but their contribution to the overall clinical effect has to be examined individually, as not only their relative pharmacological potency with regard to serotonin uptake has to be considered, but

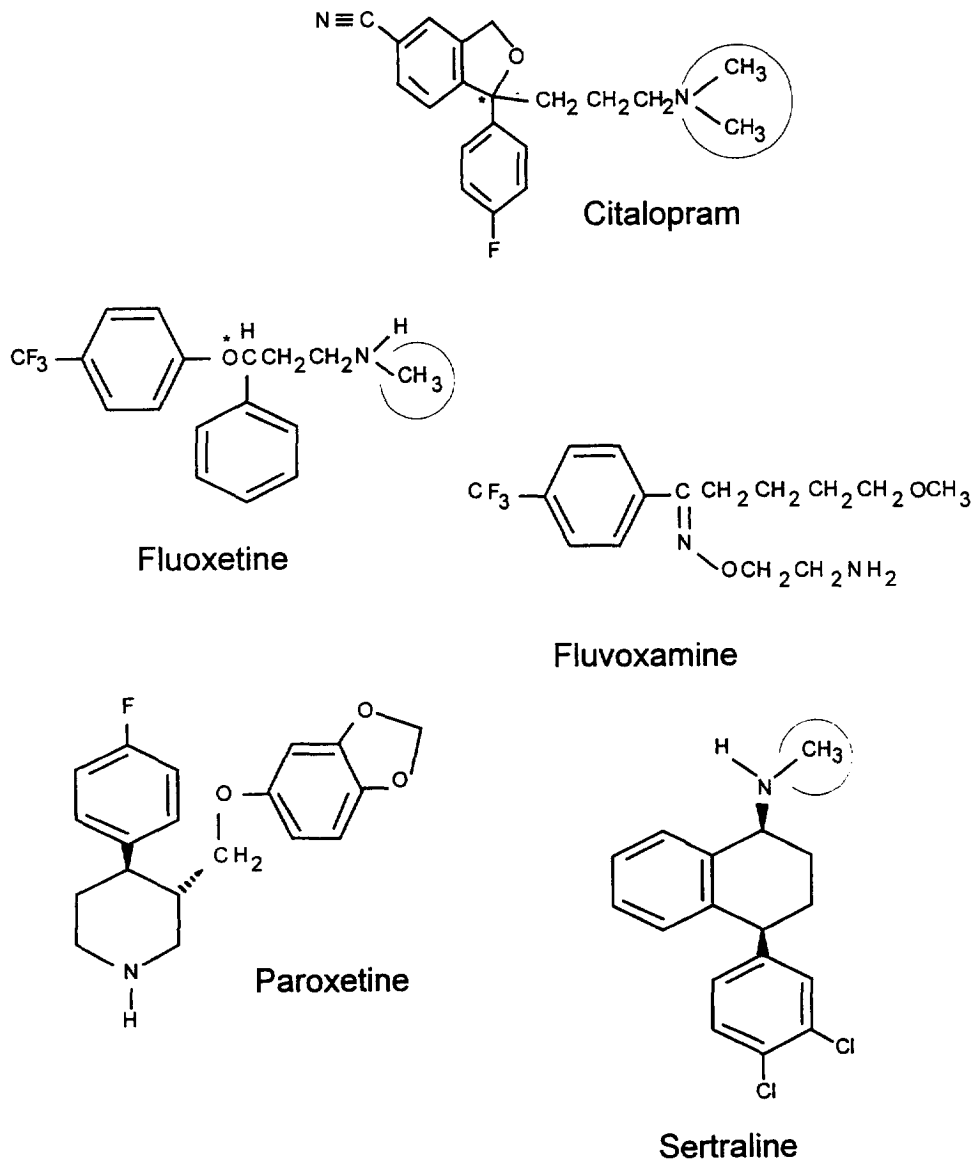

Fig. 1. Chemical structure of SSRI. ○=Site of N-demethylation. *=asymmetric center.

also their plasma levels achieved in therapeutic conditions. In the case of fluoxetine, it may be considered that (*S*)- and (*R*)-FLX, and (*S*)-NFLX but not (*R*)-NFLX are clinically relevant compounds. With regard to CIT, (*S*)-CIT and (*S*)-DCIT probably play the major role. It is only recently that some, but limited, data are available on the properties of these enantiomers. The pharmacokinetic and the pharmacodynamic properties of these five SSRIs, taking into account their metabolites and their enantiomers, have been reviewed elsewhere [18,22].

3. Analytical methods

As SSRIs differ widely in their chemical structure and as there has been, until recently, few indications to associate SSRIs [23], analytical methods for their

quantitative determination in blood have been developed individually for each drug. Methods which allow analysis of several SSRIs simultaneously would be useful for economic reasons and in cases of association of two SSRIs. There is now some evidence that they may differ in their clinical profile [24], and that in the case of nonresponse to one SSRI, a strategy based on its replacement by another SSRI or the combination of two SSRIs may be successful [23]. Almost all recent assays are based either on separation of SSRIs by high-performance liquid chromatography (HPLC) or gas chromatography (GC), but as yet, none has been published using capillary electrophoresis or immunological methods. Tables 1–5 list the different analytical methods published for the determination of SSRIs [25–70]. Several comments must be made. Firstly, in many papers, only the limit of detection (LOD) was given. We have assumed that the given value was in fact the limit of quantitation (LOQ), or the concentration at which quantitative results can be reported with a high degree of confidence [71], rather than a limit of detection, or the concentration at which an analysis is just feasible [71]. Furthermore, in very few papers were the criteria chosen to define the LOQ clearly defined (i.e. accepted signal-to-noise ratio, accepted coefficients of variation for replicate determinations, accepted deviations from the theoretical concentrations, etc.). Criteria for determining the recovery, particularly when derivatization procedures were included and presumably no derivatized standard was available, are also often lacking. Some papers state that "the method was adapted from...". Actually, the original method was developed for substances other than SSRIs and, in some instances, no apparent method revalidation was performed and such studies were therefore excluded from the table. On the other hand, in cases when a complete (rarely) or a partial (most often) revalidation has been performed, the papers were included. Several methods used other psychotropic drugs, mostly tricyclic antidepressants, as the internal standard. As most psychiatric patients are polymedicated and as some patients may benefit from an SSRI–tricyclic antidepressant combination treatment [72], such internal standards may lead to erroneous results, in particular knowing that comedications are not always correctly indicated in the dosage request form. In this regard, the use of SSRI analogues such as clovoxamine, which cannot be found in the organism, is highly recommended.

Finally, in clinical situations where plasma levels are most often measured in steady-state conditions, the analytical method should allow to measure concentrations in the lower ng/ml range. Moreover, CIT, FLUOX and SER have N-demethylated metabolites which are also SSRIs. Therefore, the laboratory which offers TDM for these compounds should use methods by which these metabolites can be measured. This is the case for most of the procedures presented in the Tables.

3.1. Citalopram

Assay procedures for citalopram and metabolites are listed in Table 1. Earlier procedures designed to measure CIT and some of its metabolites were achiral, based on their separation either by quantitative thin layer chromatography [25,26], HPLC [27–30] or GC with NPD or mass spectrometry [31]. A very recent procedure allows the determination of CIT, its two N-demethylated metabolites, its N-oxide and its propionic acid derivative, by a direct plasma injection technique and HPLC column switching procedure with fluorescence detection [32]. The development of methods suitable for the analysis of the enantiomers of CIT in plasma was made difficult by its tertiary amine structure, which does not allow its derivatization by a chiral reagent to form diastereoisomeric derivatives which could then easily be separated on an achiral column. Rochat et al. [33] have developed two HPLC methods for the assay, by fluorimetry, of the enantiomers of CIT, DCIT and DDCIT. Their separation is achieved by chiral HPLC using either a Chiracel OD [33] or a Cyclobond (Model 2000) column [34]. The first of these two methods has some disadvantages as it requires derivatization of the amines with heptafluorobutyric acid, and of the inactive metabolite citalopram propionic acid derivative with iodomethane.

3.2. Fluoxetine

Assay procedures for fluoxetine and metabolites are listed in Table 2. Methods available for FLX and NFLX are based on achiral GC with EC-detection

Table 1
Assay procedures for citalopram and metabolites

Drug, metabolites	Tissue[a] (volume in ml)	Extraction[b]	Derivatization	Separation[c] Stationary phases	Detection[d]	Recovery (%)	Range (ng/ml)	LOQ (ng/ml)	IS	Remarks	References
CIT, DCIT	P (2)	LL	Yes	TLC Anasil H	FLUO	–	50–400	20 (CIT) 50 (DCIT)	No		[25]
CIT, DCIT, DDCIT	P (2)	LL	No	TLC Merck silica gel plates	FLUO	80–90 (CIT, DCIT) 70 (DDCIT)	10–300	5	No		[26]
CIT, DCIT, DDCIT	P (1)	LL	No	*HPLC* Spherisorb ODS 5 μm	*FLUO*	>79 (*CIT*) >83 (DCIT, DDCIT)	*1–200 (CIT, DCIT)* 0.5–50 (DDCIT)	*1–2 (CIT, DCIT)* 0.5–1 (DDCIT)	*Analogue of CIT* (LU 10-202)		*[27]*
CIT, DCIT, DDCIT, CIT-P, CIT-O	P (1), U (0.2–1)	LL	No	HPLC Spherisorb ODS 5 μm	FLUO	>84 (P)	20–122 (CIT, P) 19–117 (DCIT, P) 4–27 (DDCIT, P) 12–70 (CIT-P, P) 800–4100 (CIT, U) 800–3900 (DCIT, U) 300–2100 (DDCIT, U) 300–2200 (CIT-P, U) 51–239 (CIT-O, U)	5 (P), 10–20 (U)	Analogue of CIT (LU 10-202)		[28]
CIT, DCIT	P (1–2)	LL	No	HPLC μ Bondapak C18 10 μm	UV	84 (CIT) 80 (DCIT)	10–300	5	Desipramine	Simultaneous determination of *amitriptyline*, nortriptyline, clomipramine, norclomipramine	[29]
CIT, DCIT, DDCIT	P (1–2)	SPE+LL	No	HPLC μ Bondapak C18 10 μm	UV	>70	20–200	0.8 (CIT, DDCIT) 0.7 (DCIT)	Desipramine		[30]
CIT, DCIT, DDCIT, CIT-P	P (1)	LL (CIT, DCIT, DDCI) *LL+SPE (CIT-P)*	Yes	GC Permabond SE54-DF0.25	MS (EI) or NPD	80–95 (CIT) 68–92 (DCIT) 26–41 (DDCIT) 45–65 (CIT-P)	10–500	1 (CIT, DCIT) 2 (DDCIT, CIT-P)	Methylmaprotiline Maprotiline Desmethylmaprotiline Amitriptyline acid derivative		[31]
CIT, DCIT, DDCIT, CIT-P, CIT-O	P (0.2)	Direct injection of plasma	No	HPLC Ultron N-C18	FLUO	>90 (CIT, DCIT, DDCIT, CIT-O) 50 (CIT-P)	2–150	2	Analogue of CIT (LU-202)	Column-switching procedure	[32]
(*S*), (*R*)-(CIT; -DCIT; -DDCIT; -CIT-P)	P (1)	LL	Yes	HPLC Daicel Chiracel OD	FLUO	76–80 (CIT) 70–72 (DCIT) 52–57 (DDCIT) 51–57 (CIT-P)	25–150 (CIT)[e] 5–100 (DCIT) 5–50 (DDCIT) 5–100 (CIT-P)	15 (CIT)[e] 4 (DCIT) 5 (DDCIT) 2 (CIT-P)	Methylmaprotiline Maprotiline Desmethylmaprotiline (S)-flurbiprofen	chiral column (normal mode)	[33]
(*S*), (*R*)-(CIT; -DCIT; -DDCIT)	P (1)	LL	No	HPLC Astec acetylated β-Cyclobond	FLUO	72 (CIT) 64 (DCIT) 48 (DDCIT)	5–150 (CIT)[e] 5–100 (DIT)[e] 5–50 (DDCIT)[e]	3(e)	Benzoctamine Norbenzoctamine	chiral column reverse-phase mode	[34]

CIT=citalopram, DCIT=desmethylcitalopram, DDCIT=didesmethylcitalopram, CIT-P=citalopram propionic acid, CIT-O=N-oxide citalopram, LOQ=limit of quantitation, IS=internal standard.
[a] S=serum, P=plasma, U=urine, T=tissue.
[b] LL=liquid–liquid, SPE=solid-phase extraction.
[c] HPLC=high-performance liquid chromatography, GC=gas chromatography, TLC=thin layer chromatography.
[d] FLUO=fluorimetry, MS=mass spectrometry, UV=ultraviolet, EI=electron-impact mode, NPD=nitrogen-phosphorus detector, ECD=electron capture detector, DEN=densitometric scanning after staining.
[e] The concentrations are given for each enantiomer.

Table 2
Assay procedures for fluoxetine and metabolites

Drug, metabolites	Tissue[a] (volume in ml)	Extraction[b]	Derivatization	Separation[c] Stationary phases	Detection[d]	Recovery (%)	Range (ng/ml)	LOQ (ng/ml)	IS	Remarks	References
FLX, NFLX	P (1)	LL	Yes	GC column packed with 3% SP2100 on Supelcoport 80–100 mesh	ECD	76 (FLX) 88 (NFLX)	25–800	–	4,4-bis(*p*-fluorophenyl) -N-ethylbutylamine		[35]
FLX, NFLX	S (1)	LL	No	HPLC Waters NOVA-PAK phenyl	UV	80	25–800	15	Reduced haloperidol		[36]
FLX, NFLX	S (2)	LL	No	HPLC Supelcosil LC-PCN 5 μm	UV	–	50–500	–	Protriptyline		[37]
FLX, NFLX	P (2)	LL	No	HPLC μ Bondapak C18	UV	79–86 (FLX) 55–60 (NFLX)	0–800	6	Clomipramine		[38]
FLX, NFLX	S (0.5)	SPE	No	HPLC Ultrasphere Octyl RP	FLUO	85	30–1000	20	Protriptyline		[39]
FLX, NFLX	S (1)	SPE	Yes	GC DB1 capillary column	ECD	>90 (FLX) >75 (NFLX)	20–200	–	Tomoxetine		[40]
(*S*)-, (*R*)-(FLX; -NFLX)	P (1)	LL	Yes	HPLC Jones Apex silica column 5 μm	FLUO	73	1–500[e]	1[e]	(-)-N-gamma- -(2-methylphenoxy) benzene propanamine	Chiral reagent	[41]
FLX, NFLX	P (0.25)	LL	No	HPLC RPC8 Ultrapore RPMC 5 μm	UV	79–84 (FLX) 72–73 (NFLX)	10–800 (FLX) 10–1000 (NFLX)	2	Mefloquine		[42]
(*S*)-, (*R*)-(FLX); -NFLX)	P (1–2) U (3) T (0.3–0.6)	LL	Yes	GC DB5 capillary column	ECD	–	10–1000[e]	–	I-alprenolol	Chiral reagent	[43]
FLX, NFLX	P (1)	LL	Yes	HPLC Supelcosil LC18	FLUO	79–87 (FLX) 67–77 (NFLX)	25–800	3	Maprotiline		[44]
FLX, NFLX	P (2)	LL	No	HPLC μ Bondapak C18	UV	–	0–500	–	Imipramine		[45]

FLX, NFLX	P (1)	LL	No	HPLC Resolve C18 (Z-module)	UV	>70	50–300	9 (FLX) 5 (NFLX)	Doxepine	Simultaneous determination of amitriptyline, nortriptyline, imipramine, desipramine	[46]
(*S*)-, (*R*)-(FLX; -NFLX)	P (0.5) T (0.5)	LL	Yes	HPLC Jones chromatography silica column	FLUO	86–96 (FLX) 92–93 (NFLX)	5–1000	5 (P) 25 ng/gm(T)	(*S*)-nornisoxetine	Chiral reagent Also used for determinations in tissues	[47]
FLX, NFLX	P (1)	LL	Yes	GC DB17 capillary column	ECD	76 (FLX) 88 (NFLX)	5–200	5	4,4-bis-(*p*-fluoro-phenyl)-N-ethyl -butylamine		[48]
FLX, NFLX	P (1)	LL+SPE	No	HPLC RPLC-8-DB 5 μm	UV	62 (FLX) 70 (NFLX)	20–1000	10	Protryptyline	Automated assay	[49]
FLX, NFLX	T	LL	Yes	GC 5% phenyl methyl silicone capillary column	NPD	–	50–2500	–	Maprotiline	Used only for tissues Simultaneous determinations of desipramine	[50]
(*S*)-, (*R*)-(FLX; -NFLX)	P (1)	LL	Yes	GC MN Optima 5 capillary column	MS	54-66 (FLX) 50–56 (NFLX)	5–350[e]	1[e]	Clovoxamine	Chiral reagent Simultaneous determination of fluvoxamine	[51]

FLX = fluoxetine, NFLX = norfluoxetine. For other abbreviations, see Table 1.

Table 3
Assay procedures for fluvoxamine

Drug, metabolites	Tissue[a] (volume in ml)	Extraction[b]	Derivatization	Separation[c] Stationary phases	Detection[d]	Recovery (%)	Range (ng/ml)	LOQ (ng/ml)	IS	Remarks	References
FLV	P (1)	LL	Yes	HPLC LiChrosorb RP8 7 μm	FLUO	–	100–2500	3	No		[52]
CLV	P (2)	LL	Yes	GC column packed with 5% SP2100 on Supelcoport 100–120 mesh	ECD	80	1–100	1	FLV	FLV used as IS	[53]
FLV	P (1)	LL	Yes	HPLC, TLC Zorbax Sil 7 μm on TLC plastes with silica gel 60	FLUO	99	0–200	5 (TLC) 2 (HPLC)	No	Long retention times (32 min)	[54]
FLV	P (2)	LL	Yes	HPLC Hypersil ODS 5 μm	FLUO	62–77	10–400	1.5	Metapramine		[55]
FLV	P (1)	LL	No	HPLC Nucleosil C8 5 μm	UV	93	25–400	25	CLV		[56]
FLV	P (1)	LL	No	HPLC Resolve spherical silica column 5 μm	UV	88	2–400	2	CLV		[57]
FLV	P, S (0.1)	SPE	No	HPLC Nucleosil 100 CN 5 μm	UV	97–100	25–1000	10	Oxaprotiline	Automated method with column switching	[58]
FLV	P (1)	LL	Yes	HPLC Supelcosil LC18DB 5 μm	FLUO	103–105	10–1000	10	Nortriptyline		[59]
FLV	P (2)	LL	No	HPLC μ Bondapak C18	UV	65	10–800	10	Clomiprimaine		[60]
FLV	P (1)	LL	No	HPLC Ecotube Nucleosil C8 5 μm	UV	93	0–400	10	Loxapine		[61]
FLV	P (1)	LL	Yes	GC MN Optima 5 capillary column	MS	58–59	50–500	2	CLV	simultaneous determination of (*S*)-, (*R*)-(FLX; -NFLX)	[51]

FLV=fluvoxamine, CLV=clovoxamine, FLX=fluoxetine, NFLX=norfluoxetine.
For other abbreviations, see Table 1.

Table 4
Assay procedure for paroxetine

Drug,	Tissue[a] (volume in ml)	Extraction[b]	Derivatization	Separation[c] Stationary phases	Detection[d]	Recovery (%)	Range (ng/ml)	LOQ (ng/ml)	IS	Remarks	References
PAR	P (3)	LL	Yes	GC column packed with 1.5% SP2250 on Chromosorb G-AW-DMCS, 80–100 mesh	NPD	–	–	5	Maprotiline		[62]
PAR	P (1)	LL	Yes	HPLC Spherisorb ODS 5 μm	FLUO	83–92	0–500	1	Maprotiline		[63]
PAR	P,S (0.5)	LL	No	TLC DC 60-254 Merck	DEN	–	–	3	No		[64]
PAR	S (0.5)	SPE	No	HPLC Ultrasphere Octyl RP 5 μm	FLUO	90	8–1000	5	Dibucaine		[65]
PAR	P,S (0.1)	SPE	No	HPLC Nucleosil 100 CN 5 μm	UV	107	0–500	5	Trimipramine	Automated method with column switching. Also for a PAR metabolite	[66]

PAR = paroxetine.
For other abbreviations, see Table 1.

Table 5
Assay procedures for sertraline and metabolites

Drug, metabolites	Tissue[a] (volume in ml)	Extraction[b]	Derivatization	Separation[c] Stationary phases	Detection[d]	Recovery (%)	Range (ng/ml)	LOQ (ng/ml)	IS	Remarks	References
SER	P (3)	LL	No	GC column packed with 3% Silar 10C on GasChrom Q 80–100 mesh	MS	–	1–40	1	Analogue of SER (CP-53, 631)		[67]
SER	P (1)	LL	Yes	GC SE 54 capillary column	ECD	40	1–50	1	Analogue of SER (CP-53, 630)		[68]
SER, DSER	S (1)	SPE	No	HPLC Supelco LC8 5 μm	UV	91	10–2500	10	Protriptyline	GCMS also used	[69]
SER, DSER	S (0.5)	SPE	No	HPLC Ultrasphere ODS RP 5 μm	UV	–	15–2000	10	Analogue of SER (CP-53, 630-1)		[70]

SER=sertraline, DSER=desmethylsertraline.
For other abbreviations, see Table 1.

after solid phase preextraction [40] or liquid–liquid extraction [35,48]. Some HPLC procedures do not require derivatisation, and they include UV [36–38,42,45,46,49] or fluorescence detection [39]. Nichols et al. [49] proposed an automated HPLC method. FLX and NFLX may also be derivatized with dansyl chloride before their separation by HPLC with fluorescence detection [44]. The products have been identified by positive chemical ion mass spectrometry. A procedure derived from a previously published method [37] has been described, which allows the determination of FLX and its metabolite in plasma and erythrocytes. Generally, concentrations appear to be comparable in these two blood compartments. However, the method does not take account of trapped plasma in the analytical procedure for the erythrocytes [73].

The enantiomers of FLX and NFLX may be assayed by derivatization with (*S*)-trifluoroacetylprolyl chloride and separation of the diastereoisomers on an achiral GC column (DB-5 crosslinked fused silica capillary) with their analysis by an electron capture detector [43]. By modification of this method, the enantiomers of FLX and NFLX, and FLV may be quantified in plasma [51]. The mass spectra of the derivatives obtained by this procedure are also described [51]. A stereoselective HPLC method with fluorescence detection has been found suitable for the analysis of the enantiomers of FLX and NFLX in rat brain tissue, after derivatisation with *R*-1-(1-naphthyl)ethyl isocyanate [47]. Two modifications of this procedure have been proposed for the quantitative analysis of these compounds in human plasma [41,47].

3.3. Fluvoxamine

Assay procedures for fluvoxamine are listed in Table 3. The first among the numerous methods available for FLV was actually developed for the assay of clovoxamine and it implied their derivatization and analysis by gas chromatography with electron capture detection [53]. Several HPLC methods have also been introduced, using UV detection [56–58,60,61], which do not require prior derivatization, or fluorimetric detection [52,54,55,59], which require a derivatization step. The procedure of Pullen and Fatmi [59] needs derivatisation of FLV by dansyl chloride before separation by HPLC with fluorescence detection. An automated procedure using column switching HPLC and UV detection has been described by Härtter et al. [58]. The simultaneous determination of the enantiomers of FLX and NFLX, and FLV in plasma has already been mentioned above [51].

3.4. Paroxetine

Assay procedures for paroxetine are listed in Table 4. PAR may be assayed in human plasma using GC with a nitrogen sensitive detector [62] or HPLC with fluorescence detection after derivatization with dansyl chloride [63] or without derivatization [65]. An automated method for the determination of PAR and its main metabolite includes column switching and on-line HPLC with electrochemical detection [66]. The Danish University Antidepressant Group has presented a thin layer chromatographic method for PAR in plasma [64].

3.5. Sertraline

Assay procedures for sertraline and metabolites are listed in Table 5. GC methods with electron capture detection [68] or with mass spectrometry [67] have been described for SER and DSER, as well as a HPLC method using UV detection [70]. Rogowsky et al. [69] presented a unique procedure by which SER and its metabolite may be determined in plasma both by HPLC with UV detection and gas chromatography–mass spectrometry, after purification of the extracts with copolymeric solid-phase extraction columns.

4. Conclusions

Although no therapeutic window has been defined for SSRIs, in contrast to TCAs, analytical methods for TDM of SSRIs are useful in several instances. One of its major uses may be the control of the compliance, as it has been shown that up to one third of patients stop taking their antidepressants after six weeks, and out of whom two thirds do not report it to their general practitioner [16]. The financial and social cost of such patients who may be erroneously

diagnosed as nonresponders after months of treatment and after several attempts of dose augmentation, largely outweighs, in our opinion, the cost of one or two TDM during this period. Several methods for the determination of SSRIs have been published, mostly based on GC and HPLC. However, only one method has been published which allows the simultaneous determination of two SSRIs [51]. Simultaneous analysis of several SSRIs would decrease the cost and speed of analysis but would also be useful when two SSRIs are administered simultaneously.

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