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REVIEW ARTICLE

Tools for optimising pharmacotherapy in psychiatry (therapeutic drug monitoring, molecular brain imaging and pharmacogenetic tests): focus on antidepressants

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ABSTRACT
Objectives: More than 40 drugs are available to treat affective disorders. Individual selection of the optimal drug and dose is required to attain the highest possible efficacy and acceptable tolerability for every patient.
Methods: This review, which includes more than 500 articles selected by 30 experts, combines relevant knowledge on studies investigating the pharmacokinetics, pharmacodynamics and pharmacogenetics of 33 antidepressant drugs and of 4 drugs approved for augmentation in cases of insufficient response to antidepressant monotherapy. Such studies typically measure drug concentrations in blood (i.e. therapeutic drug monitoring) and genotype relevant genetic polymorphisms of enzymes, transporters or receptors involved in drug metabolism or mechanism of action. Imaging studies, primarily positron emission tomography that relates drug concentrations in blood and radioligand binding, are considered to quantify target structure occupancy by the antidepressant drugs in vivo.
Results: Evidence is given that in vivo imaging, therapeutic drug monitoring and genotyping and/or phenotyping of drug metabolising enzymes should be an integral part in the development of any new antidepressant drug.
Conclusions: To guide antidepressant drug therapy in everyday practice, there are multiple indications such as uncertain adherence, polypharmacy, nonresponse and/or adverse reactions under therapeutically recommended doses, where therapeutic drug monitoring and cytochrome P450 genotyping and/or phenotyping should be applied as valid tools of precision medicine.

1. Introduction

More than 40 compounds are available to treat affective disorders. For selection of the optimal drug and dose, rational decision making must consider the psychopathological status of the patient and the pharmacokinetic and pharmacodynamic profiles of the drugs. Clinical decision making is therefore a complex process (Serretti 2018). Measurement of drug concentrations in blood [i.e. the use of therapeutic drug monitoring (TDM)] is most helpful in detecting individual pharmacokinetic characteristics (Hiemke et al. 2018). Major determinants of drug concentrations in blood are enzymes involved in the metabolism of drugs, primarily enzymes of the cytochrome P450 (CYP) family. Multiple variants of *CYP* genes lead to inactive, active or highly active enzymes and give rise to abnormal drug concentrations (Eap 2016). Identifying *CYP* genetic polymorphisms can therefore also be helpful in understanding and predicting interindividual pharmacokinetic variations. Positron emission tomography (PET) with specific radioligands provides insight into brain pharmacokinetics (Gründer et al. 2011). PET coupled with measurement of drug concentrations in blood enables the calculation of target molecule occupancy. When such studies have been conducted, one can extrapolate from the concentration in blood how much receptor is occupied. Binding studies on serotonin transporters and blood level measurement of selective serotonin reuptake inhibitors (SSRIs) revealed that 80% occupancy should be attained to obtain full antidepressant efficacy (Meyer et al. 2004). Brain imaging (especially PET) should

therefore be used in the early phase of drug development, while TDM and selected genotyping should be used in clinical practice to guide antidepressant drug therapy.

In the first part of this review the use of TDM, pharmacogenetics and brain imaging to optimise and/ or personalise pharmacotherapy with antidepressants will be introduced. In the second part, pharmacological and pharmacokinetic profiles, TDM, pharmacogenetics and brain imaging studies will be presented for individual antidepressant drugs, including the tricyclic antidepressants (TCAs), the SSRIs, the serotonin noradrenaline reuptake inhibitors (SNRIs), other antidepressants, and non-antidepressants (e.g. quetiapine). Specific topics such as augmentation with non-antidepressants in major depression or bipolar depression, as well as chirality will also be presented. Finally, perspectives of TDM, pharmacogenetics and brain imaging will be discussed. This review did not consider all drugs that are available to treat depression. We excluded drugs like buspirone with almost no data on TDM, pharmacogenetics or molecular imaging. This also holds true for a fixed combination of drugs (e.g. fluoxetine and olanzapine for the treatment of resistant unipolar depression).

PART 1 Introduction to therapeutic drug monitoring, pharmacogenetics and brain imaging of antidepressants

Multiple publications including review papers have been published on the use of TDM, pharmacogenetics/ pharmacogenomics and brain imaging to optimise the pharmacological treatment of patients with psychiatric

disorders. Concerning TDM, of special note is the consensus paper published by TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP or Association for Neuropsychopharmacology and Pharmacopsychiatry, hereafter referred to as AGNP) which published in-depth reviews (Baumann et al. 2004; Hiemke et al. 2011; Hiemke et al. 2018), with recommendations and reference value ranges for plasma concentrations of psychotropic drugs (Hiemke et al. 2018). These consensus guidelines were introduced in numerous clinics and laboratories and have been accepted by treating physicians. Thorough reviews have also been published on brain imaging in psychiatry and depression (e.g. Gründer et al. 2011; Ruhe et al. 2014) in addition to many recommendations on pharmacogenetic tests (e.g. Eap 2016; Genetic testing statement 2020). The aim of the present task force is to provide a comprehensive review of the current evidence on methods allowing one to assess or understand patient variability in therapy outcome. Such evidence can explain why and how brain imaging studies should be an essential part of the early clinical phase of psychoactive drug development and why and how TDM and genotyping can be useful tools in optimising the pharmacotherapy of psychiatric patients. The present review focuses on patient variability in drug metabolism of single antidepressants, reviewing the major pharmacokinetic, TDM, pharmacogenetic and brain imaging data for each drug. Essential data are summarized in Table 1. This task force is committed to providing a second review focussing on antipsychotics in the near future.

1.1. TDM for optimising antidepressant pharmacotherapy

In spite of the availability of almost 40 drugs with antidepressant efficacy, outcomes of antidepressant pharmacotherapies are so far not optimal. Most depressed patients fail to achieve or maintain response or remission under the first-line antidepressant medication (Rush et al. 2006). Other problems are related to adverse reactions. Among many possible determinants for non-response or intolerability are interpatient variability in pharmacokinetics, in particular extreme phenotypes/genotypes. A high prevalence of non-adherence to medication ranging between 10 and 60% of patients (Lingam and Scott 2002) is another obstacle in the treatment of affective disorders. As a consequence, drug levels in plasma are highly variable among individual patients. Variability in antidepressant drug metabolism was detected and reported for the first time in 1967 for

the TCAs imipramine and amitriptyline and their N-demethylated metabolites desipramine and nortriptyline, respectively (Hammer and Sjoqvist 1967). Similar observations were made later for all antidepressant drugs. This gave rise to the suggestion to use TDM as a tool to control and correct the dose of antidepressant medications individually and identify non-adherence. TDM was introduced for nortriptyline almost 50 years ago by Åsberg and co-workers (Åsberg et al. 1971) and soon extended to TCAs in general (Preskorn 1989; Perry et al. 1994) and to new antidepressant drugs more or less gradually (Ostad Haji et al. 2012). With the introduction of new antidepressant drugs, namely the SSRIs, in the 1990s the value of TDM was rated as low. The main arguments against routine TDM of SSRIs or other new antidepressants were low toxicity, large therapeutic windows and uncertain therapeutic reference ranges (Rasmussen and Brøsen 2000). TDM was regarded as justified for new antidepressants in special cases such as suspected nonadherence or drug-drug interactions.

Meanwhile, SSRIs and other new antidepressants have become first-line antidepressants. Meta-analyses of clinical trials, however, revealed similar efficacy for older and newer antidepressants (Cipriani et al. 2018). Problems of treatment failure and non-adherence still remained with the new drugs. Evidence and conviction have grown gradually that TDM should be used to optimise the treatment of affective disorders (Bengtsson 2004; Jaquenoud Sirot et al. 2006; Ostad Haji et al. 2012). With adequate use of TDM it has even been shown that direct and indirect costs of health care may be reduced (Simmons et al. 1985; Preskorn and Fast 1991; Lundmark et al. 2000; von Knorring et al. 2006; Ostad Haji et al. 2013).

TDM aims to improve efficacy and safety of drug therapies. Not only for TDM of antidepressant drugs, but for TDM in general, there is a lack of valid studies that determined optimal plasma concentrations and showed clear-cut beneficial effects of this tool. Molecular imaging, as considered in this review for antidepressant drugs, is an essential add on tool to find therapeutic ranges when based on mostly preliminary clinical trials. Optimal studies require fixed dose treatment of a sufficiently high number of real-world patients that would positively respond to a given drug. Patients must be separated according to ascending plasma drug levels into large enough subgroups with subtherapeutic, therapeutic and supratherapeutic drug concentrations. Such design allows precise definition of optimal plasma levels. Such studies, however, are logistic challenges. Nevertheless, they are urgently needed. This is particularly true in times when pharmaceutical

Table 1. Drugs available to treat depression, their major metabolites, therapeutic target sites, major enzymes of degradation, elimination half-lives and recommended therapeutic reference ranges.

Parent drugs	Active metabolites	Target sites for therapeutic action	In vivo occupancy of major target site at therapeutic concentrations	Major metabolising enzymes	Genetic polymorphisms of metabolising enzymes **	Mean t1/2 [h]	Recommended therapeutic reference ranges [ng/mL]	Conversion factors***
Agomelatine	–	MT_1 MT_2 $5\text{-}HT_{2C}$	n.d. n.d. n.d.	CYP1A2 CYP2C19 CYP2C9	Genetic polymorphism are not relevant or unknown	1.5	7–300 (Cmax)	4.11
Amitriptyline	Nortriptyline	SERT NET	n.d. 50–70%	CYP2C19 CYP2C9 CYP1A2 CYP2D6 CYP3A4	CYP2D6 CYP2C19	16 36*	80–200 (AM)	3.60 3.80*
Amoxapine	8-Hydroxyamoxapine	NET $5\text{-}HT_{2A}$	50–70% n.d.	CYP1A2 CYP2D6	CYP2D6	10 30*	200–500 (AM)	3.19 3.03*
Bupropion	Hydroxybupropion	DAT NET	20–33% n.d.	CYP2B6	CYP2B6	20 (SR) 20 (SR)*	850–1500 (Hydroxybupropion)	4.17 3.91*
Citalopram	Desmethylcitalopram Didesmethylcitalopram	SERT	80%	CYP2C19 CYP2D6 CYP3A4	CYP2C19	33 51/108*	50–110	3.08
Clomipramine	Desmethylclomipramine	SERT NET	>90%	CYP1A2 CYP2C19 CYP2D6 CYP3A4	CYP2D6 CYP2C19	21 36*	230–450 (AM)	3.18 3.32*
Desipramine	–	NET	n.d.	CYP2D6	CYP2D6	17	100–300	3.75
Desvenlafaxine	–	SERT NET	n.d. n.d.	CYP2C19 CYP3A4	Genetic polymorphism are not relevant or unknown	11	100–400	3.80
Dothiepin	Dothiepine S-oxide Northiaden	NET	n.d.	CYP2C19 CYP2D6	CYP2C19	22 19/33*	45–100	3.39
Doxepin	Nordoxepin	SERT NET	n.d. n.d.	CYP2C19 CYP2D6 CYP2C9	CYP2C19 CYP2D6	15 31*	50–150 (AM)	3.58 3.77*
Duloxetine	–	SERT NET	68–78% 30–40%	CYP1A2 CYP2D6 COMT SULT	Genetic polymorphism are not relevant or unknown	12	30–120	3.36
Escitalopram	S-Desmethylcitalopram S-Didesmethylcitalopram	SERT	75–80%	CYP2C19 CYP3A4 CYP2D6 MAO	CYP2C19	33 53/n.d.*	15–80	3.08
Fluoxetine	Norfluoxetine	SERT	92%	CYP2C9 CYP2D6 CYP2C19 CYP3A4	CYP2D6	1–4 days 7–15 days*	120–500 (AM)	3.23 3.39*
Fluvoxamine	–	SERT	80%	CYP2D6 CYP1A2	CYP2D6	15	60–230	3.14
Imipramine	Desipramine	SERT NET	n.d. n.d.	CYP2C19 CYP2D6 CYP1A2 CYP3A4	CYP2C19 CYP2D6	12 17*	175–300 (AM)	3.57 3.75*

(continued)

Table 1. Continued.

Parent drugs	Active metabolites	Target sites for therapeutic action	In vivo occupancy of major target site at therapeutic concentrations	Major metabolising enzymes	Genetic polymorphisms of metabolising enzymes **	Mean t1/2 [h]	Recommended therapeutic reference ranges [ng/mL]	Conversion factors ***
Isocarboxazid	–	MAO	n.d.	unknown	MAO	unknown	unknown	–
Levomilnacipran	p-OH-Milnacipran	SERT NET	n.d. n.d.	CYP3A4 CYP2C8 CYP2C19 CYP2D6 CYP2J2	Genetic polymorphism not relevant or unknown	12 (ER)	80–120	2.24
Maprotiline	Desmethylmaprotiline 3-Hydroxymaprotiline	NET	n.d.	CYP2D6 CYP1A2	CYP2D6	48	75–130	3.60
Mianserin	Desmethylmianserin	Alpha$_2$ 5-HT$_2$ 5-HT$_3$	n.d.	CYP1A2 CYP2D6 CYP3A4	CYP2D6	30	15–70	3.78
Milnacipran	p-OH-Milnacipran	SERT NET	< 50 % < 50 %	CYP3A4	Genetic polymorphism not relevant or unknown	8	100–150	2.24
Mirtazapine	Desmethylmirtazapine	Alpha$_2$ 5-HT$_2$ 5-HT$_3$		CYP2D6 CYP3A4 CYP1A2	Genetic polymorphism not relevant or unknown	25	30–80	3.77
Moclobemide	–	MAO-A 5-HT$_{2a}$	74–84%	CYP2C19	CYP2C19	1.5	300–1000	3.72
Nefazodone	Hydroxy-nefazodone, Triazoledione, m-Chlorophenylpiperazine	SERT	40–50%	CYP3A4 CYP2D6	Genetic polymorphism not relevant or unknown	3	unknown	–
Paroxetine	–	SERT	80%	CYP2D6 CYP3A4	CYP2D6	24	20–65	3.04
Reboxetine		NET	n.d.	CYP3A4	Genetic polymorphism not relevant or unknown	12.5	60–350	3.19
Sertraline		SERT DAT	80% n.d.	CYP2B6 CYP2C19 CYP2D6 CYP3A4 CYP2C9	CYP2B6 CYP2C19	35	10–150	3.27
Tranylcypromine	–	MAO	>58%	MAO	Genetic polymorphism not relevant or unknown	2	50–70 (Cmax)	7.51
Trazodone	m-Chlorophenylpiperazine	SERT 5-HT$_{2A}$ 5HT$_{2C}$	n.d.	CYP3A4 CYP2D6	Genetic polymorphism not relevant or unknown	6.6 (IR) 12 (ER)	700–1000	2.69
Trimipramine	Desmethyltrimipramine	SERT NET	n.d. n.d.	CYP2C19 CYP2D6 CYP2C9 CYP1A2 CYP3A4	CYP2C19 CYP2D6	24	150–300	3.40
Venlafaxine	O-Desmethyl-venlafaxine	SERT NET	80% n.d.	CYP2D6 CYP2C19 CYP3A4	CYP2C19 CYP2D6	5 (IR) 11* (IR) 15 (ER) 15* (ER)	100–400 (AM)	3.61 3.80*
Vilazodone	–					25	35–67	2.26

(continued)

Table 1. Continued.

Parent drugs	Active metabolites	Target sites for therapeutic action	In vivo occupancy of major target site at therapeutic concentrations	Major metabolising enzymes	Genetic polymorphisms of metabolising enzymes **	Mean t1/2 [h]	Recommended therapeutic reference ranges [ng/mL]	Conversion factors***
		SERT 5-HT$_{1A}$	n.d. 47–58%	CYP3A4 CYP2C19 CYP2D6	Genetic polymorphism not relevant or unknown			
Vortioxetine	–	SERT 5-HT$_3$ 5-HT$_7$ 5-HT$_{1D}$ 5-HT$_{1B}$ 5-HT$_{1A}$	35–95%	CYP2D6 CYP3A4 CYP2C9	CYP2D6	57	10–40	3.35
Augmenting drugs and bipolar depression								
Aripiprazole	Dehydroaripiprazole	D$_2$ 5-HT$_{1A}$	80%	CYP2D6 CYP3A4	CYP2D6	75 94*	40–200 (AM)	2.23
Esketamine	Noresketamine	NMDAR D2	unclear	CYP3A4 CYP2B6	Genetic polymorphism not relevant or unknown	2		–
Ketamine	Norketamine	NMDAR D2	15–20%	CYP3A4 CYP2B6	CYP2B6	2	unclear	–
Lamotrigine	–	voltage-sensitive sodium channels		UGT1A4 UGT2B7	Genetic polymorphism not relevant or unknown	25	3000–14000	3.90
Lithium	–	Second messenger system			Genetic polymorphism not relevant or unknown	24	0.5–0.8 mmol/L	–
Lurasidone	–	5-HT$_{2A}$ 5-HT$_{1A}$ D$_2$	Not available for antidepressant activity	CYP3A4	Genetic polymorphism not relevant or unknown	18	2–20[b]	2.03
Quetiapine	Norquetiapine	5-HT$_{2A}$, D$_1$ D$_2$	Not avaible for antidepressant activity	CYP3A4 CYP2D6	Genetic polymorphism not relevant or unknown	7 11*	50–100[a] 50–200[b]	2.61 3.39*

*Half-life or conversion factor of the metabolite.

**Genetic polymorphisms affecting drug concentrations and possibly clinical outcomes; source: www.pharmgkb.org/pathways (and others). Metabolising enzymes are listed from top to bottom according to their contribution, for details see text.

***Drug concentrations given in mass units can be converted to molar units by multiplication with the conversion factor (CF) nmol/L = ng/mL × CF.

[a]Reference range for augmentation in unipolar depression.

[b]Reference range for bipolar depression

Abbreviations: AM: active moiety (parent drug + active metabolite); Cmax: maximal concentration of the drug in blood; COMT: cathechol-O-methyl transferase; CYP: cytochrome P450; D$_2$: dopamine D$_2$ receptors; DAT: dopamine transporter; ER: extended release; 5-HT: 5-hydroxytryptamine receptors; IR: immediate release; MAO: monoamine oxidase; MT: melatonin receptors; n.d.: no data; NMDAR: N-methyl-D-aspartate receptor; NET: norepinephrine transporter; SERT: serotonin transporter.

industry has withdrawn from antidepressant drug discovery and the clinicians need tools to make the best out of what is currently available.

1.1.1. Antidepressant drug concentrations in plasma and clinical effects

A relation between drug concentrations in plasma and clinical outcomes is a prerequisite for TDM (Bengtsson 2004). Such relations enable determination of therapeutic reference ranges (i.e. drug concentrations required to attain good clinical efficacy associated with acceptable tolerability). For nortriptyline an inverse U-shaped relationship between plasma concentrations and clinical amelioration, with less response at both extremely low and extremely high drug levels, was found (Åsberg et al. 1971). Moreover, high concentrations of nortriptyline were associated with severe adverse effects (Åsberg et al. 1970). Significant correlations were also found between plasma concentrations and clinical effects for amitriptyline, clomipramine, imipramine and desipramine (Perry et al. 1994; Ulrich and Läuter 2002). As mentioned above, however, most studies of SSRIs and other new antidepressant drugs failed to find significant relationships. These studies, most of them retrospective analyses of flexible dose treatments, have a design that is inappropriate for establishing a concentration-response relationship (Preskorn SH 2014). In patients with major depression in need of medical treatment, the placebo response amounts to one-third of patients, while another one-third each is allotted to verum responders and non-responders, respectively (Preskorn 2014; Meister et al. 2017).

Non-response is related to many factors including heterogeneity of depression, trauma history, genetics or other factors. A significant correlation between antidepressant drug concentration in plasma and clinical improvement can be expected for the verum responders only (i.e. for one-third of the patients). Placebo responders will respond to any drug concentration and non-responders neither to low nor to high drug concentrations. These two groups give rise to marked noise and make it difficult or even impossible to identify a relationship between drug concentration and antidepressant response in the whole patient group. Even worse, in case of flexible dose studies, a negative correlation may result (Hiemke 2019). Antidepressant drug treatment usually starts with a low dose. Under such conditions, placebo responders will stay on low doses and exhibit mean low drug concentrations associated with clinical improvement. The group of later non-responders will receive high doses and exhibit

mean high drug concentrations. Since the type of response is not predictable in the whole patient group that is treated and studied, only pooled data of non-responders, placebo responders plus verum responders are obtained at the endpoint, and a negative correlation between drug concentration and improvement is the outcome of these studies (Hiemke 2019). These findings insinuate that low concentrations of the drug are more effective than high ones - a wrong conclusion based on artificial findings.

Flexible dose studies are thus not suitable for identifying an antidepressant concentration-response relationship, especially when high numbers of non-responders and placebo responders have been included. However, using fixed-dose studies with appropriate design and analysis enables identification of a concentration-effect relationship also for newer antidepressant drugs, as shown for paroxetine (Eggart et al. 2011). On the other hand, a randomised clinical trial failed to find a relationship between a concentration of paroxetine and clinical improvement (Tasker et al. 1989), but the methodology used here was inappropriate. The authors had not corrected for numbers of patients in the various concentration ranges. Doing this, a clear-cut concentration-effect relationship emerged that was fully superimposable with serotonin transporter (SERT) occupancy data obtained in humans by positron emission tomography (Eggart et al. 2011). In sum, it appears difficult to establish a concentration-effect relationship for antidepressants based on the totality of study results. However, that many studies have failed to find a significant relationship does not prove that the relationship does not exist. Absence of evidence is not evidence of absence (Altman and Bland 1995).

1.1.2. Indications for TDM of antidepressants

As specified in the AGNP consensus guidelines for TDM (Hiemke et al. 2018), plasma level monitoring may be useful for many antidepressant drugs and many indications. Its value, however, varies by drug, depending upon the drug's pharmacological properties and on patients' characteristics. With regard to antidepressants, typical indications for TDM and problems that can be solved by measuring antidepressant drug levels in plasma are as follows:

- Dose optimisation after initial prescription of the drug or after dose change for drugs with well-documented reference ranges
- Avoidance of toxic effects for drugs like TCAs with a narrow therapeutic index

- Suspected non-adherence to medication to control whether or not the patient has taken his/her medication
- Lack of improvement in controlling whether or not drug concentrations are high enough to expect improvement
- Clinical improvement concomitantly associated with adverse effects to control whether or not the dose can be reduced without the risk of losing efficacy
- Critical drug combinations for controlling pharmacokinetic drug interactions
- Clinical or physiologic conditions such as pregnancy, advanced age, hepatic and/or renal insufficiency or bariatric surgery
- Genetic conditions concerning drug metabolism, especially when drugs are substrates of CYP2D6 or CYP2C19

1.1.2. How to conduct TDM of antidepressant drugs?

Optimisation of antidepressant drug therapy by TDM requires appropriate use of the tool.

- TDM should only be requested when there is evidence that the result, the drug concentration in plasma, can support clinical decision making (see TDM indications above).
- Except in case of intoxication, plasma should be drawn under steady-state conditions (after 4 to 5 elimination half-lives) and at the time of lowest drug levels (trough level, C_{min}, usually in the morning before the next dose).
- The blood sample should be accompanied by a request form with information about the patient (most importantly demographic data, medical history of the patient, reason for request, improvement/adverse drug reactions, dose and dosing schedule of the drug to be assayed, time of blood sampling in relation to last drug intake, co-medication)
- The laboratory should use validated methods that are regularly controlled by internal and external controls
- Results should be reported within 48 h at the latest after plasma sampling to optimally support clinical decision making
- Concentrations of the drug and relevant metabolites should be reported with reference ranges
- Expert interpretation and pharmacological advice should be provided with every assessment,

especially in case of complex medication and specific problems indicated in the request form.

More detailed information on the practice of TDM of antidepressant drugs is given in the consensus guidelines of the TDM task force of the AGNP (Hiemke et al. 2018), whose aim was to summarise the state of the art of TDM for distinct older and newer antidepressant drugs.

1.2. Genotyping for optimising antidepressant pharmacotherapy

Variability in drug response might be related to variability in a drug's pharmacokinetics (absorption, distribution, metabolism and excretion) leading to changes in obtained drug plasma concentrations and also to variability in a drug's pharmacodynamics, i.e. of drug's targets, enzymes, receptors and transporters (Crettol et al. 2014; Eap 2016).

1.2.1. Pharmacokinetic genes for personalised drug selection

Cytochrome P450 (CYP) isoforms control the metabolism of a large number of psychotropic drugs with CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 metabolising more than 90% of all drugs. The Food and Drug Administration (FDA) table of pharmacogenetic markers in drug labelling (Table of Pharmacogenomic Biomarkers in Drug Labeling 2018) contains more than 239 drugs, of which 30 are used in psychiatry (17 antidepressants). Among those drugs, there is a high proportion of FDA-approved pharmacogenetic information incorporated in the labels (for psychotropic drugs almost all labels concern CYP2D6, some of them also CYP2C19). An updated table of pharmacogenetic associations has very recently been published by the FDA (Table of pharmacogenetic associations 2020), the list being open for comments. The European Medicine Agency (EMA) and other regulatory agencies in the world (e.g. Canada, Japan) have also re-labelled drugs providing pharmacogenetic information (Drug Label Annotations 2019). One can mention that eliglustat, for the treatment of the rare Gaucher disease, is the first drug with a mandatory *CYP2D6* test before starting the treatment. However, for psychotropic drugs, none of those labels are yet asking for pharmacogenetic tests to be performed before initiating treatment. Thus, for example, the FDA-approved drug label for pimozide, an antipsychotic, states that *CYP2D6* genotyping *should* be performed at doses above 0.05 mg/kg/day

in children or above 4 mg/day in adults while for carbamazepine, an antiepileptic and mood stabiliser, the label states that patients with ancestry in genetically at-risk populations *should* be screened for the presence of HLA-B*15:02 or HLA-A*31:01 prior to initiating treatment.

CYP2D6 activity varies between poor, intermediate, extensive (normal) and ultrarapid metabolizers (PM, IM, EM and UM), with PM having no functional alleles, IM being heterozygous for a fully functional 'active' and an inactive allele or having two alleles with reduced activity, EM being 'wildtype' with two active alleles, and UM having an amplification of functional alleles (3 to 13 copies) (Bertilsson et al. 2002; Hicks et al. 2013). More than 100 variants and sub-variants have been described for *CYP2D6* (CYP2D6 allele nomenclature 2015; The PharmVar Consortium 2019) with a strong influence of geography and ethnicity, which have therefore to be taken into account in genotyping and its interpretation (Gaedigk et al. 2017). A large number of studies showed the strong influence of CYP2D6 activity on the pharmacokinetics of many antidepressants (Bertilsson et al. 2002; Stingl and Viviani 2015; Hicks et al. 2017). The activity of CYP2D6 can be inhibited by other drugs, with a potential to transform the phenotype of a CYP2D6 UM, EM or IM into a PM (Jaquenoud Sirot et al. 2006). On the other hand, CYP2D6 activity appears not to be induced in contrast to other CYP isoenzymes, although indirect induction through inflammation suppression by tocilizumab or tumour necrosis factor inhibitors has been suggested (Cytochrome P450 2D6 2020).

The first genotype-based dose recommendations for antidepressants were proposed by Kirchheiner et al. in 2001 (Kirchheiner et al. 2001), followed by other more recent working groups who publish periodic updates and develop guidelines linking the results of pharmacogenetic tests to specific therapeutic dose recommendations. Two examples are the Dutch Pharmacogenetics Working Group from the Royal Dutch Association for the Advancement of Pharmacy (DPWG) developed guidelines (Swen et al. 2011) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) (Hicks et al. 2013; PharmGKB 2016), with efforts to compare and harmonise guidelines between DPWG and CPIC (Caudle et al. 2020). Personalised dosing in psychiatry based on CYP genotype is best adapted for TCAs because of their narrow safety margins (Hicks et al. 2013). However, TCAs are rarely prescribed nowadays, being mainly used at low doses for chronic neuropathic pain and migraine prevention, although TCAs have an important place in treatment algorithms in some

countries, such as the Netherlands (Spijker and Nolen 2010). Personalised dosing according to *CYP2D6* genotype has also been proposed for more recent antidepressants such as SSRIs or SNRIs (Stingl and Viviani 2015; Hicks et al. 2017). However, their wider margin of safety in overdose as well as lower risk for serious side effects decrease the specificity and sensitivity of CYP genotyping tests for increasing therapeutic response and/or preventing side effects. Higher prevalence of psychotropic drug-induced side effects have been found to be associated with the CYP2D6 PM status (Lessard et al. 1999; Sallee et al. 2000; Brockmoller et al. 2002; Tamminga et al. 2003; Rau et al. 2004; de Leon et al. 2005; Penas-Lledo et al. 2013), while studies investigating associations between CYP2D6 phenotype and/or genotype and treatment response were mainly negative (Gex-Fabry et al. 2008; Peters et al. 2008; Serretti et al. 2009), despite some positive studies (Lobello et al. 2010). Of note, expert recommendations have been published by CPIC for CYP2D6 and CYP2C19 genotypes for dosing of TCAs and SSRIs (Hicks et al. 2013; Hicks et al. 2015; Hicks et al. 2017).

The *CYP2C19* gene is also highly polymorphic with more than 30 described variants, and also with a strong influence of ethnicity on minor allele frequencies. Similarly to the way CYP2D6, PM, IM, EM and UM have been described, the UM phenotype possibly results from the enhanced gene transcription from the *17 allele. Personalised prescribing based on CYP2C19 has been proposed for some SSRIs (Hicks et al. 2015; Fabbri et al. 2018), CYP2C19 activity being particularly important for citalopram/escitalopram metabolism, drug exposure and therapeutic failure (Jukic et al. 2018). Interestingly, CYP2D6 and CYP2C19 have been suggested to be involved in the production or metabolism of endogenous compounds (Kirchheiner et al. 2005; Snider et al. 2008; Bertilsson 2010) which, by involvement in neurodevelopment, could lead to possible variations in personality, neurocognitive function and vulnerability to psychopathology including suicidality for CYP2D6 (Bertilsson et al. 1989; Zackrisson et al. 2010; Penas-Lledo et al. 2011; Stingl and Viviani 2011; Penas-Lledo and Llerena 2014) and depressive symptoms for CYP2C19 (Jukic et al. 2017). It is not known whether such variations could contribute to variabilities in drug response and side effects. In any case, based on the limited amount of studies, CYP2D6 and CYP2C19 genotyping or phenotyping cannot be used as predictors of psychiatric symptoms and/or disorders.

CYP2B6 metabolises fewer compounds, notably bupropion and to some extent sertraline among

antidepressants. *CYP2B6* is highly polymorphic, with variants associated with multiple mechanisms (transcriptional regulation, splicing, mRNA and protein expression, and catalytic activity) (Zanger and Klein 2013). The simultaneous combinations of many variants producing multiple haplotypes, in addition to the large ethnic influence on *CYP2B6* polymorphism, complicates its analysis and interpretation.

CYP1A2 is particularly involved in the metabolism of agomelatine and duloxetine and, to a lesser extent, of fluvoxamine. In some cases, *CYP1A2* variants have been associated with low or high CYP1A2 activity (Abernethy and Kerzner 1984; Allorge et al. 2003) but these alleles are either rare or with low predictive value. In addition, CYP1A2 activity (and of other CYP isoforms such as CYP3A) is also controlled by other genetic factors, including nuclear receptors and the P450 oxido-reductase (Dobrinas et al. 2011; Dobrinas et al. 2012; Thorn et al. 2012). Thus, even combining the result of *CYP1A2* genotyping with other genetic factors, also taking into account smoking status (CYP1A2 is inducible and smoking is the most significant environmental factor increasing CYP1A2 activity), is currently of little help in most subjects and phenotyping tests (*in vivo* measurement of the activity using a probe substance such as caffeine) (Bosilkovska et al. 2014) or TDM appear more appropriate for personalised dosing of CYP1A2-dependent drugs.

CYP3A, a term that in adults reflects the collective activity of CYP3A4, CYP3A5, and CYP3A7, (the latter mainly foetal but expressed after birth in some individuals), is involved in the metabolism of more than 50% of marketed drugs. There is a large overlap of activity among the various CYP3A isoforms which potentially reduces the influence of genetic heterogeneity of individual *CYP3A* genes on the pharmacokinetics of CYP3A-dependent drugs, a deficiency of one isoform being potentially partially compensated by the activity of others. For the *CYP3A4* gene, the *CYP3A4*20* loss-of-function allele has been found in 1.2% of the Spanish population (Apellaniz-Ruiz et al. 2015), while the *CYP3A4*22* allele, associated with low hepatic CYP3A4 expression and CYP3A4 activity, has been found in 5 to 7% in the Caucasian population (Elens et al. 2013). For the *CYP3A5* gene, the *CYP3A5*3* allele causes alternative splicing and protein truncation and results in the absence of CYP3A5 activity, *CYP3A5* being more frequently expressed in the livers of African Americans (60%) than in those of Caucasians (33%) (Kuehl et al. 2001). Although cases of CYP3A poor metabolizers, with the simultaneous occurrence of mutations in different isoforms which leads to very low or null CYP3A activity,

have been described, genotyping is of little clinical relevance (Eap, Buclin, Hustert, et al. 2004) and, as for CYP1A2, estimation of CYP3A activity is best measured by phenotyping tests [e.g. using a very low oral dose of midazolam (Eap, Buclin, Cucchia, et al. 2004; Bosilkovska et al. 2014) or by TDM]. Indeed, phenotyping tests and TDM also integrate the influence of variations of several other genes modulating the expression of *CYP3A* genes (such as the hepatocyte nuclear factor or pregnane X receptor genes) and of the large influence of environmental factors, including drugs and/or xenobiotics and/or diet-inducing or -inhibiting CYP3A activity (Tracy et al. 2016).

Other pharmacokinetic genes, in particular *ABCB1*, encoding for the permeability P-glycoprotein (PGP), have been investigated in many studies but with mixed results. The PharmGKB site attributes a low level of evidence [level 3 out of 4: annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association] for the association between *ABCB1* polymorphisms with efficacy and/or toxicity and/or adverse drug reactions for several antidepressants (ABCB1 Clinical Annotations 2020). Therefore, there is a lack of evidence for the clinical use of *ABCB1* genotyping in psychiatry at present (Bruckl and Uhr 2016; Bschor et al. 2017).

1.2.2. Pharmacodynamic genes for personalised drug selection

For antidepressants, genetic variations of serotoninergic mediators (e.g. SERT, and serotonin (5HT) receptors) as well as of intracellular signal transduction pathways have also been extensively studied (Porcelli, Fabbri, et al. 2011), some of them mentioned in the relevant sections of the present review.

Due to inhibition of the reuptake of serotonin by the SERT by many antidepressants, polymorphisms of the SERT gene (*SLC6A4*) have been extensively studied, mainly on the 's' (short) and 'l' (long) alleles, although there is limited understanding of the phenotypic-genotypic relationship (de Leon 2016). A meta-analysis of 33 studies confirmed the association between the (l)-allele (associated with a two-fold higher expression) and response and remission to SSRIs in Caucasians (Porcelli et al. 2012), but with a modest clinical impact of *SLC6A4* genotyping (OR: around 1.5), and, therefore, of little clinical benefit for predicting response. A modest clinical impact of *SLC6A4* polymorphisms on antidepressant response, with OR between 1.5 and 2.0, has been confirmed in a recent meta-analysis (Ren et al. 2020). Other genes, including serotonin receptors (*HTR1A*, *HTR2A*), tryptophan hydroxylase (*TPH1*)

involved in serotonin biosynthesis, *STin2* influencing SERT expression, and brain-derived neurotrophic factor (*BDNF*), are probably involved in antidepressant action, and may also modestly modulate antidepressant response (Kato and Serretti 2010). The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in antidepressant response, and polymorphisms in *FKBP5*, which regulates glucocorticoid receptor sensitivity, has been associated with rapid response to antidepressant treatment (Binder et al. 2004). This study was, however, followed by both positive and negative results (Sarginson et al. 2010). A meta-analysis of 3 genome wide association studies (GWAS), namely GENDEP, MARS and STAR*D, examining the association with antidepressant drug response in 2256 individuals of Northern European descent with major depressive disorders (MDD), failed to identify reliable predictors of antidepressant treatment response (Gendep Investigators et al. 2013). For reviews discussing the associations between genetic polymorphisms of pharmacodynamic genes with antidepressant response more extensively, please see (Hickie and Rogers 2011; Porcelli, Drago, et al. 2011; Fabbri et al. 2014).

1.2.3. Polygenic tests

Because of the ease of genetic analysis and the frequent polygenic influence on a drug's response, the future of pharmacogenetics resides in multi-gene tests, both at the pharmacokinetic and pharmacodynamic levels. Concerning pharmacokinetic genes, multi-gene tests allow one to take into account the multiple metabolic pathways implicated in the pharmacokinetics of drugs. Such tests are, however, complementary and cannot substitute for TDM, which takes the actual serum concentration into account regardless of genetic and environmental factors (e.g. strong inhibition or induction of metabolism by drugs, food and/or xenobiotics). A recent review proposed a minimum gene and allele set for pharmacogenetic testing in psychiatry that includes 16 variant alleles within five genes (CYP2C9, CYP2C19, CYP2D6, HLA-A, HLA-B), with CYP2C19 and CYP2D6 being relevant for antidepressants (Bousman et al. 2019), tests for these five genes being presently reimbursed by Medicare and Medicaid in the US. It must to be mentioned, however, that there is presently no consensus among all actors in the field (Goldberg 2017), as well as questions about the lack of demonstrated of cost-effectiveness of pharmacogenetic tests in the treatment of depression (Rosenblat et al. 2017). A recent study using a commercially available multi-test in a large patient- and rater-blinded randomised controlled study showed that pharmacogenetic testing (both for

pharmacokinetic genes including *CYP2D6*, *CYP2C19* and *CYP1A2* and pharmacodynamic genes including *SLC6A4* and *HTR2A*) improves response and remission rates (Greden et al. 2019a). However, the analytical as well as the clinical validity of the test used in the study has been questioned previously (de Leon 2016), also taking into account the abovementioned remarks on genotyping of *CYP1A2* and of pharmacodynamic genes. The study raised several other concerns (Goldberg et al. 2019; Greden et al. 2019b; Severance et al. 2019) in addition to the fact that the treating clinicians in the study arm were not blinded. Other multi-tests have also been proposed by many other commercial companies (see (Zeier et al. 2018)), with a lack of transparency concerning the algorithms used for recommendations of prescriptions, and without data supporting the tests' clinical validity and utility (de Leon 2016). There is need for transparency with regard to which genes/alleles/polymorphisms are analysed and included in a pharmacogenetic test, together with the corresponding evidence, both for single and polygenic tests. Such transparency is necessary as it will allow for re-evaluation of the results of earlier-performed genotyping tests and recommendations based on them, in the light of new knowledge. The FDA thus recently warned against the use of many genetic tests with unapproved claims predicting patient response to specific medications (FDA version 11.1.18). It subsequently also issued a warning letter to a genomics lab for illegally marketing a genetic test that claims to predict patients' responses to specific medications (FDA version 4.4.19). On commenting on this letter, CPIC has stressed that the only pharmacogenetic tests which can help dosing some antidepressants are CYP2D6 and CYP2C19 testing (Hicks et al. 2020). Therefore, based on the abovementioned arguments, the use of such tests cannot presently be recommended, also in agreement with a review concluding that there are presently insufficient data to support the widespread use in clinical practice of combinatorial pharmacogenetic decision support tools integrating multiple genetic variants, although there are clinical situations in which this technology may be informative, in particular for side-effects (Zeier et al. 2018). Future studies are needed to allow evidence-based implementation of pharmacogenetic tests into routine clinical practice in psychiatry.

1.3. Brain imaging for optimising antidepressant pharmacotherapy

Functional brain imaging technology, especially nuclear imaging methods (PET; Single Photon Emission

Computed Tomography, SPECT) have been used extensively since the mid-1980s to study the pharmacokinetics and pharmacodynamics of psychotropic drugs; PET especially represents a routine tool in drug development for the assessment of target engagement (Wong et al. 2009; Gründer et al. 2011). While, at a given dose, plasma concentrations of psychotropic drugs vary to a large extent because of large inter-individual differences in absorption, distribution, metabolism, and excretion, PET (and, to a lesser extent, SPECT) allows for the characterisation of the relationships between occupancy of target molecules in the brain (neurotransmitter receptors and transporters) and plasma concentration of the respective drug. Major progress has been made in correlating these measures with clinical efficacy and side effects. In addition, PET provides important information about the time course of the relationship between plasma levels of a drug and the proportion of target molecules occupied over time. This allows for elucidation of the brain pharmacokinetics of psychotropic drugs, thereby providing further guidance for drug dosing and the establishment of therapeutic reference ranges for TDM.

PET occupancy studies are based on the principle that a cold (i.e. unlabeled) drug (the pharmaceutical under consideration) displaces a radioactively-labelled radiotracer, which binds to the target molecule at trace concentrations (Gründer et al. 2011). Of note, in the presence of active metabolites which occupy the same receptor (or transporter), the occupancy measured by PET is that of both the parent compound and its metabolites. The extent of this displacement is related to the baseline binding of the radiotracer in the unblocked state. Thus, the radioactivity in the target region in the blocked versus the unblocked state provides the target occupancy (in percent) as follows:

$$\text{Occupancy } [\%] = 100 - \left[\left(\frac{\text{Receptor Availability}_{\text{blocked}}}{\text{Receptor Availability}_{\text{unblocked}}} \right) \times 100 \right]$$

Since it is not always possible to study patients with psychiatric disorders in a medication-free state, patients are sometimes studied in the blocked state only. In such circumstances unblocked baseline data are taken from normal control samples, assuming that patients and controls are not (or only marginally (Ruhe, Booij, Reitsma, et al. 2009)) different in receptor availability at baseline.

This paradigm has been most extensively applied to the group of antipsychotics. For this class of drugs, relationships between dopamine D_2 receptor occupancy

and serum concentrations on the one hand and clinical efficacy and (specifically extrapyramidal) side effects on the other hand are well established (Gründer et al. 2009). It has to be mentioned that PET techniques allow to measure occupancy of targets in the brain by drugs, but in the case of receptors, they cannot inform on their pharmacodynamics, i.e. whether they are agonists, partial agonists or antagonists.

The situation for antidepressants varies by target. The sample size required to differentiate clinical response across different doses is much greater in depression than in schizophrenia. Hence, randomised, double blind study designs with different occupancies for assessing the relationship of occupancy to clinical response are lacking, which is a limitation for occupancy studies across all antidepressant targets. Instead, the strategy taken has been to characterise occupancy for doses associated with clinical response, an approach best suited when multiple selective antidepressants are available as well as optimal radioligand development. For the SERT, the occupancy threshold is better established, given the availability of various SSRIs and very good radioligand development (Meyer et al. 2004), whereas for the noradrenaline transporter (NET), a reasonably exact threshold is difficult to establish due to greater difficulty in the development of high quality NET radiotracers and, to some extent, to the lack of selective noradrenaline reuptake inhibitors (NRI). Optimal threshold occupancies for dopamine transporters (DAT) and monoamine-oxidase A (MAO-A) are based upon characterisation of clinical doses of bupropion and moclobemide, respectively. However, due to the limited availability of therapeutics, even though excellent radiotracers have been developed for these targets, little evidence about the relationship between target occupancy and clinical efficacy is available.

The available literature for the TCA clomipramine illustrates the need for an in-depth study of the brain pharmacokinetics of antidepressants in relation to their plasma levels on the one hand and to their clinical effects on the other hand (Gründer et al. 2011): Clomipramine acts preferentially on the SERT, whereas its main metabolite desmethylclomipramine is a relatively selective NET inhibitor. In the only available PET study, the compound has been shown to occupy 80% of the SERT at doses as low as 10 mg, with a calculated median (ED$_{50}$; dose estimated to provide half-maximal occupancy) of less than 3 mg and an EC$_{50}$ (plasma concentration estimated to provide half-maximal occupancy) of 1.42 ng/mL (Suhara et al. 2003). Doses of 25 mg daily almost completely occupy the SERT. These observations are in sharp contrast to the

fact that the clinically used clomipramine doses are 50–150 mg per day. Even much higher doses are sometimes used in patients suffering from obsessive-compulsive disorder (Foa et al. 2005). According to the AGNP, therapeutic plasma concentrations of clomipramine plus desmethylclomipramine are in the range of 175–450 ng/mL (Hiemke et al. 2018). These profound discrepancies raise serious questions about the validity of the clinical studies upon which therapeutic doses and plasma concentrations of the TCAs are based. In contrast, if the therapeutic doses and plasma concentrations are correct, they challenge the notion that the SERT is the molecular target through which TCAs exert their antidepressant effects. In addition, the available PET studies also call into question the hypothesis that bupropion, classified as a noradrenaline and dopamine reuptake inhibitor, really exerts its clinical effects through monoamine reuptake inhibition (Meyer et al. 2002).

Pharmacological MRI (phMRI) has been used for the elucidation of the mode of action of antidepressants and response prediction (Harmer et al. 2006), and intensive research is ongoing, but information useful for individual patients cannot yet be derived from those studies. It would go beyond the scope of this article to cover all of these aspects. In this article, only those PET studies are being discussed that relate target engagement (receptor or transporter occupancy) to plasma concentrations of the respective drug, because such studies are extremely helpful in determining therapeutic reference ranges (see above). In addition, while phMRI studies always provide information on e.g. response prediction on a group level, PET studies on target engagement are able to relate occupancy values to plasma levels with an unsurpassed accuracy, i.e. on a single subject level. Thus, different from fMRI studies, PET studies on target engagement today represent an essential part of many drug development programs, because they provide crucial information for dose finding.

2. Pharmacological and pharmacokinetic profiles, TDM, pharmacogenetics and brain imaging studies for individual antidepressant drugs

2.1. TCAS

2.1.1. Amitriptyline, nortriptyline

Amitriptyline is a TCA with mixed serotonin and nor-adrenaline reuptake inhibition effect. The major metabolic pathway of the tertiary amine amitriptyline is the N-demethylation by CYP2C19 to form the secondary amine nortriptyline, which is the main active metabolite. Other CYP enzymes involved in the formation of nortriptyline include CYP2C9, CYP1A2, CYP2D6 and CYP3A4 (Venkatakrishnan et al. 1998). Both amitriptyline and nortriptyline are metabolised to less active 10-hydroxy metabolites mainly by CYP2D6 and to a lesser extent by CYP3A4 (Breyer-Pfaff 2004). Mean elimination half-life ($t_{1/2}$) is 16 h (range 10–25 h) for amitriptyline and 36 h (range 16–56 h) for nortriptyline (Preskorn SH 1986). Amitriptyline has similar reuptake inhibitory potencies for serotonin and noradrenaline, whereas nortriptyline is preferentially a noradrenaline reuptake inhibitor (NRI). Amitriptyline has higher affinities for muscarinic cholinergic receptors and histamine H_1 receptors than nortriptyline (Sanchez and Hyttel 1999). *CYP2C19* genotype impacts the ratio of amitriptyline to nortriptyline plasma concentrations (Jiang et al. 2002), which may modulate antidepressant activity and side effects.

Amitriptyline and nortriptyline, similar to TCAs, show a wide range of inter-individual variability in metabolism (10–30 fold) and elimination rates (Preskorn SH 1986). The same dose can lead to sub-therapeutic, therapeutic or toxic plasma concentrations depending on individual patient characteristics. The therapeutic index for these compounds is small, with a correlation between serum concentrations and major adverse effects related to central nervous system and cardiac toxicity (Preskorn SH 1989). To evaluate the relationship between amitriptyline serum concentration and its therapeutic effect in depression, Ulrich et al. (Ulrich and Läuter 2002) have performed a comprehensive survey and meta-analysis. Analysis of the pooled data from 27 studies with adequate design confirmed a therapeutic window of the sum of trough serum concentrations of amitriptyline and nortriptyline of 80–200 ng/mL which is in agreement with the AGNP, with a recommendation level 1 (level 1: strongly recommended; level 2: recommended; level 3: useful; level 4: potentially useful) for TDM (Hiemke et al. 2018). Since co-medications with inhibitors of CYP2D6 or CYP2C19 will lead to increased plasma concentrations and combinations with CYP and/or PGP inducers such as St. John's wort or rifampicin will lead to decreased drug concentrations, dose adaptation under TDM control is required (Hiemke et al. 2018). Elderly and young patients differ in the pharmacokinetics of amitriptyline. Therefore, TDM is recommended for these patients. Amitriptyline and nortriptyline plasma concentrations are not influenced by renal function while dose adaptations should be performed

in case of liver insufficiency, and TDM is recommended (Hiemke et al. 2018).

Therapeutic failure or adverse drug reactions may be linked to CYP2C19 and/or CYP2D6 genetic variations that can alter the amitriptyline/nortriptyline ratio and/or drug clearance, respectively. In clinical studies, higher amitriptyline plasma concentrations were observed in CYP2D6 PMs based on debrisoquine (a CYP2D6 substrate) metabolic ratio, in patients with two variant CYP2C19 alleles compared to patients with no variants, and in patients homozygous for the non-functional CYP2C19*2 allele compared to wild-type patients. Higher amitriptyline and lower nortriptyline plasma concentrations were measured in CYP2C19 PMs compared to EMs and in CYP2C19 IMs compared to EMs. The number of functional CYP2C19 alleles had a significant influence on the metabolic ratio of amitriptyline to nortriptyline. A higher risk of side effects has been observed in patients with at least one non-functional CYP2D6 allele compared to those with two functional alleles and, among patients taking TCAs, the risk of switching to another antidepressant was higher in CYP2D6 PMs than EMs (Hicks et al. 2013).

In 2001, based on the evidence available at that time, Kirchheiner et al. (Kirchheiner et al. 2001) proposed that CYP2D6 PMs should receive about 50% and EMs about 120% of the recommended amitriptyline dose in the summary of product characteristics. CYP2C19 PMs should receive 60% and EMs 110% of the recommended dose. More recently, the Pharmacogenetics Working Group from the Royal Dutch Association for the Advancement of Pharmacy (Swen et al. 2011) proposed that an alternative drug should be selected for CYP2D6 UMs and PMs. For CYP2D6 IMs, a 25% amitriptyline dose reduction was recommended. The CPIC recommends considering an alternative drug for CYP2D6 or CYP2C19 UMs and for CYP2D6 PMs. For CYP2D6 IMs and CYP2C19 PMs, 25% and 50% dose reductions are recommended, respectively. The CPIC also proposed amitriptyline dosing recommendations for combined CYP2D6 and CYP2C19 phenotypes, but these recommendations were classified as optional due to the sparse clinical evidence for an additive effect of CYP2D6 and CYP2C19 on tricyclic dosing.

The binding of amitriptyline to a molecular target in the human or non-human primate brain has not been studied. Two PET studies on the occupancy of the NET by nortriptyline have been published, one after single doses in six healthy volunteers (Sekine et al. 2010) and one after chronic administration in ten patients suffering from depression (Takano et al.

2014). Single oral doses of 10–75 mg nortriptyline occupied between 16% (10 mg) and 41% (75 mg) of the NET in the thalamus (Sekine et al. 2010). From these values, the authors calculated an ED_{50} of 76.8 mg and an EC_{50} of 59.8 ng/mL. Patients with depression were treated with doses in the range of 75–200 mg for a duration of at least one month (Takano et al. 2014). The observed occupancy of the NET was between 50% and 70%, with only a modest increase in occupancy with increasing doses. The estimated ED_{50} and EC_{50} values required to occupy 50% of the NET were 65.9 mg/day and 79.8 ng/mL, respectively. Differences in those values between the two studies are most likely due to differences in dosing (single versus multiple doses). The two available PET studies suggest that at the lower end of the therapeutic reference range proposed by the AGNP (70–170 ng/mL (Hiemke et al. 2018) the NET is occupied to approximately 50% by nortriptyline. Interestingly, however, at 170 ng/mL, the upper level of the reference range, NET occupancy is just slightly higher (about 60%), and even at the highest plasma concentrations (321 ng/mL) previously reported (Takano et al. 2014) the NET occupancy did not exceed 70%.

2.1.2. Amoxapine

Amoxapine, a dibenzoxazepine antidepressant, is the demethylated metabolite of the antipsychotic loxapine. Amoxapine has been reported to have an onset of clinical action earlier than that of other TCAs. It also retains antipsychotic activity at a considerably reduced level. Amoxapine inhibits the reuptake of noradrenaline, but is very weak against serotonin uptake. Moreover, the drug has been shown to decrease the density of 5-HT$_{2A}$ receptors and to be a highly potent antagonist at this receptor (Kobayashi A et al. 1992). It also blocks the dopamine D$_4$ receptors much more potently than the dopamine D$_2$ receptors (Apiquian et al. 2003). The mean $t_{1/2}$ is 9.8 ± 2.6 h (Calvo et al. 1985). Two major metabolites exist in the plasma of subjects: 8-hydroxyamoxapine (mainly formed by CYP1A2; $t_{1/2}$ 30 h), which is pharmacologically active, and 7-hydroxyamoxapine (mainly formed by CYP2D6), to which most of the side effects are attributed (Selinger et al. 1989).

As the clinical efficacy of the drug may depend on the steady-state plasma concentrations of amoxapine and 8-hydroxyamoxapine, both substances should be measured (Kobayashi A et al. 1992). The ratios of 8-hydroxy amoxapine/amoxapine range from 0.5 to 9.7, indicating a wide range of concentrations of both

compounds (Beierle and Hubbard 1983) in agreement with the described wide interindividual variations in concentration levels of the drug and its metabolites (Selinger et al. 1989). The therapeutic reference range for amoxapine plus 8-hydroxyamoxapine is reportedly 200–500 ng/mL (Tasset and Hassan 1982). No dose recommendations for amoxapine according to pharmacogenetic data could be found in the literature.

Occupancy of the SERT or the NET, through which amoxapine supposedly exerts its antidepressant effects, has not been determined in the human or non-human primate brain. In order to characterise amoxapine's putative ('atypical') antipsychotic actions, binding to D_2 dopamine and 5-HT_2 receptors has been studied in healthy volunteers who received $50 - 250$ mg amoxapine for five days (Kapur et al. 1999). Above plasma levels of approximately 20 ng/mL, 5-HT_{2A} receptors were almost completely blocked. Even at the highest plasma levels attained in that study (51 ng/mL), the D_2 receptor occupancy did not exceed 70% in the striatum, and it only gradually increased from approximately 50% at 20 ng/mL to around 70% at 50 ng/mL (Kapur et al. 1999).

2.1.3. Clomipramine

Clomipramine is a TCA drug with a strong serotonin reuptake inhibition effect and a weaker noradrenaline reuptake inhibition. Clomipramine is metabolised to desmethylclomipramine, which is a strong inhibitor of noradrenaline reuptake. Furthermore, clomipramine is an antagonist of muscarinic, H_1, α_1 adrenergic and 5HT_{2A} receptors. $t_{1/2}$ is 16–60 h (mean value of 21 h) for clomipramine and 36 h for desmethylclomipramine, with steady state reached after 1–2 weeks (Hiemke et al. 2018). Clomipramine is metabolised to desmethylclomipramine primarily by CYP2C19 but also by CYP3A4 and CYP1A2. Desmethylclomipramine but also clomipramine are both metabolised to inactive metabolites by CYP2D6. Drug-drug interactions might occur with inhibitors of CYP2C19, CYP3A4, CYP2D6 and CYP1A2 and with inducers of CYP1A2 and CYP3A4 (Gillman 2007) and a wide range of inter-individual variability in metabolism and elimination rates of clomipramine has been shown (Balant-Gorgia et al. 1991). The clomipramine/desmethylclomipramine ratio can be altered by fluvoxamine, a strong CYP1A2 and CYP2C19 inhibitor, resulting in an increased plasma level of clomipramine, thereby increasing the serotonergic activity of clomipramine (Szegedi et al. 1996).

The AGNP strongly recommends the use of TDM for clomipramine dose titration and for special indications (level 1), with a therapeutic reference range of clomipramine plus desmethylclomipramine of 230–450 ng/mL (Hiemke et al. 2018). This range was obtained from controlled clinical trials showing beneficial effects of therapeutic drug monitoring (Hiemke et al. 2018). The lower threshold of 230 ng/mL has predictive value regarding the occurrence of response (Gex-Fabry et al. 1999).

The DPWG has, based on 10 papers comprising 272 patients, recommended for CYP2D6 PMs a 50% dose reduction with TDM of clomipramine and desmethylclomipramine (Swen et al. 2011). For CYP2D6 IMs, data are insufficient to allow calculation of dose adjustment, and TDM of clomipramine and desmethylclomipramine is recommended. For CYP2D6 UMs TDM is also recommended, or an alternative drug such as citalopram or sertraline should be selected. For CYP2D6 PMs, IMs and UMs, the clomipramine maintenance dose should be adjusted based on clomipramine and desmethylclomipramine plasma concentrations (Swen et al. 2011). The CPIC (Hicks et al. 2013) cited 6 clinical studies linking CYP2D6 and/or CYP2C19 phenotype/genotype with clomipramine metabolism. In a clinical study with 244 patients treated with clomipramine, no significant associations were shown between *CYP2C19* and *CYP2D6* genetic variants and clomipramine or desmethylclomipramine plasma concentrations (de Vos et al. 2011). In a clinical dose-effect study in 109 patients, PMs had a significantly higher desmethylclomipramine plasma concentration and a significantly higher clomipramine plus desmethylclomipramine plasma concentration (Danish University Antidepressant Group (DUAG) 1999). In another clinical study in 25 healthy volunteers, CYP2D6 PMs had significantly lower clearance of clomipramine (Nielsen et al. 1994). In terms of clinical impact, a clinical study in 45 depressed Caucasian patients treated with clomipramine showed a significant association between reported side effects and slow metabolism by CYP2D6 (Vandel et al. 2004). To our knowledge, besides a case report showing that ultrarapid metabolism of clomipramine, as confirmed by CYP2D6 genotyping, is the likely explanation for therapy resistance in a depressive patient [5431], no studies have reported associations between *CYP2D6* or *CYP2C19* polymorphisms and clinical response to this drug. Based on the available literature, no polymorphism other than *CYP2D6* and *CYP2C19* is consistently relevant to prescription of clomipramine in daily practice.

In one study, clomipramine was administered in single doses ($5 - 50$ mg) to healthy volunteers and chronic doses ($20 - 250$ mg/day) to patients with depression (Suhara et al. 2003). Single doses of 5 mg clomipramine

occupied almost 70% of the SERT, 10 mg blocked 80%, and higher doses led to occupancies of 85–90%. Subchronic dosing in patients revealed almost complete saturation of the SERT at daily doses of just 20 mg. From the patient data, these authors calculated an ED_{50} of 2.6 mg and an EC_{50} of 1.40 ng/mL. Values calculated from the single dose studies were very similar. These values are strikingly lower than the clinically used doses and the plasma levels recommended by the AGNP (Hiemke et al. 2018). The binding of clomipramine to the NET has not been studied with imaging in humans but in two cynomolgus monkeys (Takano et al. 2011). Clomipramine and desmethylclomipramine were separately administered intravenously. Calculated mean EC_{50} values were 24.5 ng/mL for clomipramine and 4.4 ng/mL for desmethylclomipramine. The reported ED_{50} values were related to the monkeys' body weight, but with 0.44 mg/kg (clomipramine) and 0.11 mg/kg (desmethyl-clomipramine) were assumed to be very low. These values also suggest that NET occupancy is quite high under clinically used doses in humans.

2.1.4. Dothiepin (dosulepin)

Dothiepin, a TCA and a thio-analogue of amitriptyline (Rydzynski 1966), has been shown to have potent antidepressant and anxiolytic properties with minimal side effects (Lipsedge et al. 1971; Johnson et al. 1973; Lambourn and Rees 1974). Its antidepressant activity is mediated through facilitation of noradrenergic neurotransmission by uptake inhibition (Ishikawa et al. 1986) and possibly also by enhancement of serotoninergic neurotransmission (Lancaster and Gonzalez 1989). The anticholinergic actions of TCAs such as dry mouth, constipation, dizziness, tachycardia and palpitation are less pronounced with dothiepin than imipramine and amitriptyline (Lambourn and Rees 1974; Sim et al. 1975). Dothiepin has a mean $t_{1/2}$ of 22 h (range 14–40 h) while those of its two main metabolites are 19 h (13–35 h) for dothiepin S-oxide, the major metabolite, while that for northiaden is 33 h (22–60 h).

The AGNP level of recommendation for use of TDM for dothiepin is 2, with a therapeutic reference range of 45–100 ng/mL (Hiemke et al. 2018).

The major enzyme involved in dothiepin metabolism is CYP2C19 (Attia et al. 2012) and to a lesser extent CYP2D6 (Yu DK et al. 1986). Although CYP2C19 wild-type (WT) had high metabolic activity for dothiepin metabolism, the E72K mutation of CYP2C19 (Glu72→Lys72) decreases enzymatic activity by 29–37%, while binding affinities were diminished 2.5- to 20-fold (Attia et al. 2012; Attia et al. 2014). On the other hand, low activity and low affinity of CYP2C9 WT

is recovered notably by a K72E mutation (Attia et al. 2014). Consequently, the intrinsic clearance values for CYP2C9 K72E were significantly higher than those for CYP2C9 WT. The position of the mutation was identical for CYP2C19 and CYP2C9, implying that the residue may be important in tricyclic metabolism. No dose recommendations for dothiepin on the basis of pharmacogenetics data could be found in the literature.

There is no published report on the binding of dothiepin to a molecular target in the human or non-human primate brain.

2.1.5. Doxepin, nordoxepin

Doxepin is a TCA drug inhibiting serotonin and noradrenaline reuptake, with a very high affinity for histamine H_1-receptors and a lower affinity for muscarinic receptors. Doxepin is applied as a mixture of Z-isomer (15%, more active) and E-isomer (85%, less active) (Kirchheiner et al. 2001). The major metabolic pathways of doxepin are N-demethylation by CYP2C19 to nordoxepin, an active metabolite, and the hydroxylation of doxepin as well as nordoxepin by CYP2D6 to 2-hydroxy(nor)doxepin, which are inactive metabolites. CYP2C9 has also been shown to be involved in doxepin metabolism (Venkatakrishnan et al. 1998). Mean $t_{1/2}$ is 15 and 31 h for doxepin and nordoxepin, respectively.

Although no clear relationship between serum concentrations and therapeutic response has been shown, responders seem to have higher serum concentrations than nonresponders (Leucht et al. 2001). The AGNP level of recommendation for use of TDM for doxepin is 2 with a therapeutic reference range of 50–150 ng/mL for doxepin plus nordoxepin (Hiemke et al. 2018). TDM of doxepin is recommended in cases of liver insufficiency, but is not necessary in case of renal insufficiency.

The DPWG recommends for CYP2D6 UMs an increase of doxepin dose by 100%, or the choice of an alternative drug such as citalopram or sertraline (Swen et al. 2011). For CYP2D6 IMs and PMs, 20% and 60% doxepin dose reductions are recommended, respectively. In addition, for CYP2D6 PMs, IMs and UMs, the maintenance dose should be adjusted based on doxepin and nordoxepin plasma concentrations (Swen et al. 2011).The CPIC cited four clinical studies and two in vitro studies to substantiate their recommendations. The in vitro studies demonstrated, with a high level of evidence, that the formation of nordoxepin was correlated to CYP2C19 enzymatic activity (Härtter et al. 2002) and that metabolism of doxepin, particularly the E-isomer, was correlated to CYP2D6 enzymatic activity (Haritos et al. 2000). In a clinical study

with 42 healthy volunteers, several significant correlations were shown between the number of *CYP2D6* non-functional alleles and oral clearance (decrease), plasma concentration (increase), and $t_{1/2}$ (increase) of doxepin and nordoxepin. An association was also found between the number of *CYP2C19* non-functional alleles and oral clearance (increase) of doxepin (Kirchheiner et al. 2002). In another clinical study with 25 healthy volunteers, CYP2D6 UMs had significantly lower Cmax and AUC of doxepin and nordoxepin in comparison to EMs (Kirchheiner et al. 2005).

There are no published reports on the binding of doxepin or nordoxepin to a molecular target in the human or non-human primate brain. Doxepin labelled with carbon-11 has been intensively used as a PET tracer for quantification of the histamine H1 receptor (Funke et al. 2013).

2.1.6. Imipramine, desipramine

Imipramine is a TCA with mixed serotonin and noradrenaline reuptake inhibition effect. The major metabolic pathway is the N-demethylation by CYP2C19 to form the secondary amine desipramine, with a preferential NRI and with a stronger drive-enhancing effect (desipramine had for decades been available as a TCA by itself but has been withdrawn). Other less important CYP enzymes involved in this formation of desipramine include CYP3A4 and CYP1A2. Both imipramine and desipramine are metabolised to 2-hydroxy metabolites mainly by CYP2D6 (Rudorfer and Potter 1999), which are subsequently glucuronidated and readily eliminated by renal excretion along with the non-conjugated hydroxyl forms (Potter and Manji 1990). The elimination half-lives range from 11–25 h for imipramine and 15–18 h (mean 17 h) for desipramine, which explains their high interindividual variability of steady-state plasma concentrations (Hiemke et al. 2018).

Because of the wide range of inter-individual variability in metabolism and elimination rates and the toxicity of TCAs in overdose, the AGNP recommends the use of TDM for imipramine and desipramine with a level of recommendation of 1 and with a therapeutic reference range of 175–300 ng/mL for imipramine plus desipramine and 100–300 ng/mL for desipramine alone (Hiemke et al. 2018). In a meta-analysis, evidence for a curvilinear relationship was found with a combined therapeutic reference range between 175–350 ng/mL (imipramine plus desipramine) and a decreasing response at plasma levels above 350 ng/mL. A response with plasma levels below 150 ng/mL is considered unlikely to occur (Perry et al. 1994; Birkenhager et al. 2005).

Expectedly, *CYP2D6* genotypes (also considering the number of functional alleles) and *CYP2C19* genotypes have been associated with variations of imipramine and desipramine metabolism (Hicks et al. 2017). As CYP2D6 PMs present decreased metabolism of imipramine and desipramine as compared to EMs, they have an increased risk for side effects and require a reduction in dose. Similarly, CYP2C19 PMs have decreased metabolism of imipramine as compared to CYP2C19 EMs (for detailed references of the original publications, see (Hicks et al. 2017). Kirchheiner et al. first proposed that CYP2D6 PMs should receive 30% of the recommended imipramine or desipramine dose, while CYP2D6 EMs should receive 130% of the recommended imipramine dose and may require much higher than average desipramine doses, in combination with TDM being particularly important in this subgroup (Kirchheiner et al. 2001). Concerning CYP2C19, genotype-based dose recommendations advise 60% of the average dose for PMs and 100% for EMs (Kirchheiner et al. 2001). More recently, the PWG proposed for imipramine, along with TDM, dose reductions for CYP2D6 PMs (70%), CYP2D6 IMs (30%) and CYP2C19 PMs (30%), while an alternative drug or a dose increase of 70% is recommended for CYP2D6 UMs (Swen et al. 2011). The CPIC recently recommended considering an alternative drug for CYP2D6 or CYP2C19 UMs and PMs. Dose reductions and TDM are also recommended for CYP2D6 IMs (25%) and CYP2D6 or CYP2C19 PMs (50%). Similar recommendations apply for desipramine and *CYP2D6* genotypes (PharmGKB 2016; Hicks et al. 2017) and dosing recommendations for combined CYP2D6 and CYP2C19 phenotypes are also proposed.

There is no published report on the binding of imipramine to a molecular target in the human or non-human primate brain. Desipramine was also not systematically evaluated. The drug was used as a blocking agent in PET studies of new radioligands for the NET (Jang et al. 2013), but from those studies, mostly performed in a very small number of monkeys, conclusions relevant to the treatment with desipramine of patients cannot be drawn.

2.1.7. Trimipramine

Trimipramine is a chiral TCA of which the mechanism of action remains unclear, as it does not or only weakly inhibits noradrenaline or serotonin reuptake at therapeutic doses (Berger and Gastpar 1996). Trimipramine is metabolised to the main metabolites desmethyltrimipramine, didesmethyltrimipramine, 2-hydroxy trimipramine and 2-hydroxy desmethyltrimipramine (Suckow

and Cooper 1984). Desmethyltrimipramine is considered to show pharmacological activity similar to the demethylated metabolites of other tricyclic antidepressants. CYP2D6 appears to be involved in the hydroxylation of trimipramine and desmethyltrimipramine while CYP2C19 and CYP2C9 appear to be involved in the demethylation pathway of trimipramine. Similar to other TCAs, CYP1A2 and CYP3A4 could also contribute to trimipramine metabolism (Eap, Bender, et al. 2000; Kirchheiner, Müller, et al. 2003). Mean $t_{1/2}$ is 24 h and peak plasma levels are reached after 2–4 h (Lapierre 1989).

Few studies have examined the correlation between plasma levels and clinical improvement, either showing no significant correlation (Cournoyer et al. 1987; Simpson et al. 1988) or associating therapeutic response to delusional depression with trimipramine concentrations higher than 160 ng/mL (Frieboes et al. 2003). The AGNP level of recommendation to use TDM is 2 with a therapeutic reference range of 150–300 ng/mL for trimipramine (Hiemke et al. 2018).

CYP2D6 and CYP2C19 genotypes have been associated with variations of trimipramine metabolism. A correlation was observed between the number of functional CYP2D6 alleles and its metabolism. CYP2D6 and/or CYP2C19 PMs have an increased risk for side effects and require a decreased dose of trimipramine (Eap, Bender, et al. 2000; Kirchheiner, Müller, et al. 2003; Kirchheiner, Sasse, et al. 2003). The CPIC recently updated its guideline for CYP2D6 and CYP2C19 genotypes and dosing of TCAs (Hicks et al. 2017) and (PharmGKB 2016). For the treatment of depression with trimipramine, the CPIC recommends considering an alternative drug for CYP2D6 or CYP2C19 UMs and PMs. Dose reductions and TDM are also recommended for CYP2D6 IMs (25%) and CYP2D6 or CYP2C19 PMs (50%). Dosing recommendations for combined CYP2D6 and CYP2C19 phenotypes are also proposed for trimipramine and others for TCAs. The overall evidence is classified as 'optional' for trimipramine.

There are no published reports on the binding of trimipramine to a molecular target in the human or non-human primate brain.

2.2. SSRI

2.2.1. Citalopram, escitalopram

The SSRI citalopram, a racemic mixture of S- and R-citalopram, has a very low affinity for noradrenaline and dopamine reuptake (Hyttel et al. 1992), and its serotonin reuptake inhibition property is mainly exerted by the S-enantiomer escitalopram. Citalopram is metabolised to active metabolites desmethylcitalopram and didesmethylcitalopram primarily by CYP3A4, CYP2C19 (citalopram to desmethylcitalopram) and CYP2D6 (desmethylcitalopram to didesmethyl citalopram) (Sindrup et al. 1993; Kobayashi K et al. 1997; Rochat et al. 1997; von Moltke et al. 1999; Shelton et al. 2020). The mean $t_{1/2}$ of citalopram has been reported to be 33 h (Kragh-Sorensen et al. 2009) and, in a study with only EMs of CYP2D6 and CYP2C19, $t_{1/2}$ was 51 h for desmethylcitalopram and 108 h for didesmethylcitalopram (Sidhu et al. 1997). The range of the $t_{1/2}$ is, however, wide for both the parent compound and metabolites. An extensive inter-individual concentration variation among patients on the same daily dose is expected, whereas the concentration variation over time within the same patient is significantly smaller (Reis et al. 2003; Jukic et al. 2018).

In the elderly a prolonged $t_{1/2}$, reduced clearance and, subsequently, significantly higher serum citalopram concentrations than in younger patients have been shown. Clearance values as well as the desmethylcitalopram/citalopram ratios seems to decrease with increasing age. This indicates reduced metabolic activity in elderly patients (Fredericson Overo et al. 1985; Reis et al. 2007). A dose reduction is not warranted in patients with moderately impaired renal function. However, a dose reduction in patients with severe renal failure is recommended. Likewise, a dose reduction is recommended in patients with impaired hepatic function due to a significant decrease in citalopram clearance and an approximately twofold increase in $t_{1/2}$ (Joffe et al. 1998).

Citalopram and escitalopram have the potential to prolong the QT interval to a significant extent in contrast to other SSRIs; thus, being a CYP2C19 PM could be a risk factor when treated with citalopram or escitalopram (Funk and Bostwick 2013). High citalopram doses have been associated with QT prolongation and authorities such as the FDA and EMA recommend a restricted maximum daily dose of 40 mg/day in adults, and 20 mg/day in the elderly, in patients with impaired liver function and in patients who are PMs of CYP2C19 or taking CYP2C19-inhibiting concomitant medication. None of the regulatory warnings include the need to measure serum concentrations of citalopram. Even though no statistical correlation was found between the citalopram dose or serum concentration level and QTc prolongation, it has been suggested that CYP2C19 phenotype may be helpful in predicting QTc prolongation (Kumar et al. 2014).

The main metabolic pathway of escitalopram is N-demethylation to S-desmethylcitalopram, primarily

catalysed by CYP2C19 and to a lesser extent by CYP3A4 and CYP2D6. Further demethylation to S-didesmethylcitalopram is predominantly carried out by CYP2D6 (Sangkuhl et al. 2011). The metabolites are not considered to contribute to the antidepressant effects, escitalopram is 7 and 27 times more potent than S-desmethylcitalopram and S-didesmethylcitalopram, respectively, in serotonin reuptake inhibition (Waugh and Goa 2003)). Escitalopram binds to the primary reuptake inhibitory site on the SERT and has a distinct effect on an allosteric binding site (Sogaard et al. 2005). The R(-)-enantiomer has no pharmacological effect on its own but counteracts some of the activity of the S(+)-enantiomer (Mork et al. 2003; Sanchez et al. 2004), probably by an allosteric effect on the binding of escitalopram to the SERT. Half-life ($t_{1/2}$) in serum for escitalopram and S-desmethylcitalopram is 32.5 h and 54.1 h, respectively (Sogaard et al. 2005). The adverse event profile for escitalopram seems to be similar to that of citalopram (Waugh and Goa 2003). Although there have been regulatory warnings for both citalopram and escitalopram, the latter apparently has less influence on QT prolongation than the former, regardless of CYP2C19 phenotype (Thase et al. 2013), as both enantiomers have the same potency for blocking the hERG channel (Hasnain et al. 2013) and as escitalopram is prescribed at half the dose of the racemate.

The AGNP level of recommendation for the use of TDM for citalopram and escitalopram is 1 with a therapeutic reference range of 50–110 ng/mL for citalopram and 15–80 ng/mL for escitalopram (Hiemke et al. 2018). A recent study suggests that not only citalopram but also its N-demethylated metabolite contributes to the antidepressant effect of citalopram. Patients with a significant reduction in depression scores exhibited concentrations above 73 ng/mL for N-desmethylcitalopram (Ozbey et al. 2018)

Many studies have shown the impact of CYP2C19 pheno/genotypes on the pharmacokinetics of citalopram and escitalopram, both after single and multiple doses and in different ethnic groups (Sangkuhl et al. 2011; Huezo-Diaz et al. 2012; Chang M et al. 2014; Hicks et al. 2015; Jukic et al. 2018). A systematic review and meta-analysis including 847 patients and 140 volunteers from 16 pharmacokinetic studies showed that PMs had 95% higher and UMs (carriers of two *17-alleles) 36% lower exposure compared to the EMs (Chang M et al. 2014). Most interestingly, a recent large ($n = 2087$) study showed that, in comparison to the CYP2C19 EM group, switches from escitalopram to another antidepressant within 1 year were 3.3, 1.6, and

3.0 times more frequent among the PMs, the rapid (*1/*17) and ultrarapid (*17/*17) groups, respectively (Jukic et al. 2018). CPIC (Swen et al. 2011) suggests a 50% reduction in starting dose in PMs of CYP2C19 followed by dose titration to response, or an alternative drug not predominantly metabolised by CYP2C19. In UMs, an alternative drug not predominantly metabolised by CYP2C19 is recommended. In contrast, the DPWG gives no dose recommendations for PMs but titration of citalopram/escitalopram dose in UMs to a maximum of 150% based on TDM, response and adverse drug effects (Swen et al. 2011). CYP2D6 genotype alone has not been shown to influence the exposure to escitalopram. However, in a small Spanish study, a 23% difference in citalopram exposure was found between EMs and IMs of CYP2D6, the difference being more clear in subjects who also carried defective CYP2C19 alleles (Fudio et al. 2010). Severe adverse effects leading to study withdrawal and an estimated very long $t_{1/2}$ of citalopram was reported in one healthy volunteer who was a PM for both CYP2C19 and CYP2D6 (Herrlin et al. 2003). No dose recommendations based on CYP2D6 genotype can be given.

Initially the only neuroimaging method for detecting SERT occupancy was [123I]2-beta-carbomethoxy-3-beta-(4-iodophenyl)-tropane (β-CIT) SPECT. A study compared 5-HTT binding in a combined thalamus-midbrain region in 13 patients with MDD who had been treated for at least one week at dosages between 20–60 mg/day of citalopram with 11 controls, using [123I]β-CIT SPECT (Pirker et al. 1995), reporting a 50% decrease in [123I]β-CIT binding. With this technique another study reported similar occupancies of 51% and 39% after 8 days of treatment with 40 mg/day citalopram (Kugaya et al. 2003). However, [123I]β-CIT SPECT has equal affinity for SERT and DAT (Laruelle et al. 1994); hence, it would be expected that unblocked DAT in the ventral tegmentum and the substantia nigra within the brainstem result in an underestimation of drug occupancy. No difference in binding was observed between 20 mg/day and 40 mg/day and it is plausible that the lack of a within-subject design reduced the power to detect dos-related effects, given the inherent between-subject variability of 5-HTT binding, and effects of season and sex on this measure (Ruhe, Booij, Reitsma, et al. 2009).

A major leap forward in neuroimaging occurred in the year 2000 with the advent of [11C]DASB. Across two datasets [11C]DASB PET was applied in a within-subject design, measuring 5-HTT BP_{ND} (binding potential BP_{ND}, ND = non-displaceable) before and after 4 weeks of citalopram treatment in 18 subjects (Meyer,

Wilson, et al. 2001; Meyer et al. 2004). These studies reported an occupancy of 81% in striatum with similar occupancies across the prefrontal cortex, anterior cingulate cortex, thalamus and midbrain after treatment with the minimum therapeutic dose (20–40mg). The study included occupancy assessment from doses of 1 mg to 60 mg daily and a nonlinear plot was fitted to the striatal occupancy relationship to plasma concentration indicating an ED_{50} of 3.4 mg/day and an EC_{50} of 11.7 ng/mL with considerable plateauing of occupancy at plasma concentrations above 60 ng/mL although a theoretical maximum occupancy of 96% was suggested by the fitting. Consistent with this finding and the plateauing of the occupancy to plasma concentration relationship, the same group (Voineskos et al. 2007) reported a striatal SERT occupancy of $85 \pm 2\%$ in 4 MDD-patients who received citalopram 60–80 mg/day for ≥ 4 weeks compared to controls in a between-subject design.

To date, it appears that similar occupancies are found in young and old patients: 7 geriatric MDD-patients (mean age 65 ± 5yrs) were investigated with [^{11}C]DASB PET after treatment with citalopram 20–40mg/day for 8–10 weeks (Smith et al. 2011). SERT-occupancy was 73% in the striatum and 76% in the thalamus.

Very short durations of treatment are associated with somewhat lower SERT occupancy. In a single oral dose study of citalopram (20 mg), occupancies ranging from 66 to 78% were reported (Lundberg et al. 2007), which were approximately 5% lower than corresponding values reported with the same dose by a previous study during longer treatment (Meyer, Wilson, et al. 2001). Sixteen male controls treated with citalopram at different dosages (10–60 mg/day) were investigated for different durations (2–7 days) to validate [^{123}I]-ADAM SPECT (Erlandsson et al. 2005). Maximum SERT-occupancy in the midbrain was 84%. Based on their results, the authors questioned whether the variability of estimated occupancy values may be too high for critical assessment of SERT-occupancy by SSRI with [^{123}I]-ADAM, although they concluded [^{123}I]-ADAM might still be used to assess whether putative SSRIs achieve maximal SERT-occupancy at therapeutic doses. Thirteen MDD-patients who received one week of citalopram at 10 mg/day were investigated, of which 11 improved within one week and seven were responders ($\geq 50\%$ decrease of symptoms) were investigated (Herold et al. 2006). With [^{11}C]-ADAM SPECT a mean midbrain SERT-occupancy of citalopram of 61% was determined after one week, although with a high individual variability (37–88%).

In sum, citalopram given at the minimal ED_{50} 20–40 mg/day for at least four weeks yields approximately 80% SERT occupancy. Interestingly, SERT occupancy appears to be somewhat lower when citalopram is administered in a single dose or early in treatment. One key area for future study is occupancy investigations in the elderly although, to date, the relationship of dose to SERT occupancy relationship seems similar to younger subjects. Other useful future directions include development of additional downstream target measurements of SERT occupancy, and investigation of occupancy in other diseases besides MDD. Discrepancies between early studies with (β-CIT) SPECT and later investigations can be accounted for by specific binding to the DAT (Laruelle et al. 1994), although these initial studies were important for empirically demonstrating brain penetration by citalopram. Finally, the effects of higher doses of citalopram on SERT occupancy levels are small and seem to be consistent with the observation that higher doses are only slightly more effective than lower doses (Jakubovski et al. 2016; Furukawa et al. 2019).

With escitalopram being the active enantiomer, it would be expected that the R-enantiomer would have lesser occupancy and possibly interfere with occupancy by the S-enantiomer because the R-enantiomer binds to a low-affinity allosteric site on SERT (Mansari et al. 2007). Differences between escitalopram and R,S citalopram occupancy were investigated (Kasper et al. 2009) by combining two previous [^{123}I]-ADAM SPECT occupancy studies in 25 and 15 healthy male controls (Klein et al. 2006; Klein et al. 2007). By comparing the occupancy dose relationship of citalopram (R- and S-enantiomer) and escitalopram (S-enantiomer only) during acute and prolonged treatment, it could be shown that, although doses were equivalent, prolonged treatment for 10 days with escitalopram 10 mg/day resulted in significantly higher occupancy rates ($82 \pm 5\%$) than with citalopram 20 mg/day ($64 \pm 13\%$; $p < 0.01$). A particularly interesting finding in this set of studies was that a comparison of the plasma level of escitalopram with occupancy suggested that greater occupancy occurred relative to plasma level when only the single enantiomer was present (Klein et al. 2006; Klein et al. 2007). Reasonable consistency across studies was found insofar as the numerical contribution of the R-enantiomer to SERT occupancy was minimal (and almost negligible) in a [^{11}C]MADAM PET study comparing SERT occupancy between single dose R,S-citalopram at 20 mg and escitalopram at 10 mg (Lundberg et al. 2007).

Nineteen MDD-patients were studied with [^{11}C]DASB PET both 6 h after the first dose of escitalopram (10 mg/day) or citalopram (20 mg/day) and after 3 weeks of continued treatment at these dosages (Lanzenberger et al. 2012). Of note, although these two drugs contain equal amounts of escitalopram, plasma and brain levels of escitalopram might not necessarily be equivalent after in vivo administration. Data were pooled with a focus on the escitalopram content administered. The single dose of SSRIs led to a significant reduction in striatal SERT availability, resulting in regional occupancies with a mean of 70 ± 5% (range 60%–78%). An intriguing finding was that greater ratio of baseline SERT binding in the amygdala/hippocampus complex, subgenual anterior cingulate cortex and habenula relative to the SERT binding in the median raphe nuclei (MRN), as measured after the first dose, was positively predictive of a response after ≥3 weeks of escitalopram treatment (Lanzenberger et al. 2012).

In summary, there is some evidence that escitalopram at 10 mg/day yields approximately 75–80% SERT occupancy after 3 weeks at the lowest clinically ED$_{50}$ of 10 mg daily. The contribution of the R-enantiomer is minimal after a single dose, and possibly modestly interferes with the occupancy of the S-enantiomer after chronic dosing. Ideally, additional studies evaluating the relationship between higher escitalopram doses and occupancy would be desirable, as would be studies evaluating escitalopram on downstream targets.

2.2.2. Fluoxetine

Fluoxetine was the first SSRI that became available for clinical use in the United States and is administered as a racemic mixture of (R)- and (S)-fluoxetine. It undergoes extensive metabolic conversion, leading to the active metabolite norfluoxetine and to multiple other metabolites with no clinical relevance. Norfluoxetine has similar potency and selectivity of 5-HT uptake inhibition that is similar to its parent compound (Altamura et al. 1994). The N-demethylation of fluoxetine to norfluoxetine has been suggested to be mediated by CYP2D6 and CYP2C9, with lesser contributions from CYP3A and CYP2C19, but few studies have investigated its metabolism and the results have been inconclusive (Hiemke and Härtter 2000). Furthermore, the role of other enzymes which contribute to more than 70% of the biotransformation of fluoxetine is so far obscure (Hiemke and Härtter 2000).

Fluoxetine has a long t$_{1/2}$ of 1 to 4 days and it is even longer for norfluoxetine, ranging from 7 to 15 days (Altamura et al. 1994). Fluoxetine exhibits nonlinear kinetics with longer t$_{1/2}$ and reduced oral clearance under multiple dosing compared with single doses (Altamura et al. 1994). Age, sex, weight and renal impairment do not affect fluoxetine pharmacokinetics, while hepatic dysfunction led to significantly prolonged t$_{1/2}$ and a lower clearance (Altamura et al. 1994). Fluoxetine and norfluoxetine are potent inhibitors of CYP2D6 and moderate inhibitors of CYP2C9, whereas they have a mild to moderate effect on the activity of CYP2C19 and CYP3A4 (Spina et al. 2008). Thus, fluoxetine has high potential for clinically relevant pharmacokinetic interactions which may continue for weeks after the discontinuation of treatment due to the long t$_{1/2}$ of norfluoxetine (Spina et al. 2008).

No clear relationship between response and the plasma concentration of either fluoxetine, norfluoxetine or the sum of both has been found (Hiemke and Härtter 2000; Rasmussen and Brøsen 2000). However there are a few studies that suggest an optimal response in depressive patients with concentrations of fluoxetine and norfluoxetine less than 500 ng/mL (Rasmussen and Brøsen 2000). The AGNP level of recommendation for the use of TDM for fluoxetine is 3 with a therapeutic reference range of 120–500 ng/mL for the sum of fluoxetine and norfluoxetine (Hiemke et al. 2018). Therefore, TDM may be useful mainly in situations where poor compliance is suspected, when therapeutic failure or toxic events are experienced with therapeutic doses or for patients with liver impairment (Rasmussen and Brøsen 2000).

Both enantiomers of fluoxetine and the active metabolite S-norfluoxetine are substrates of CYP2D6 with PMs displaying a significant increase of AUCs as compared to EMs in single-dose studies (Zhou 2009). Dose-adjusted plasma concentrations of fluoxetine have been associated with a number of *CYP2D6* active genes (Llerena et al. 2004) and, despite conflicting results (Serretti et al. 2009), *CYP2D6* polymorphism may contribute to variability of fluoxetine pharmacokinetics (Blazquez et al. 2012). Based on a scarce dataset, a dose adjustment of 50 to 70% for PMs and 110 to 120% for EMs has been proposed (Kirchheiner, Nickchen, et al. 2004). No data is available, however, to support the influence of *CYP2D6* genotype on clinical outcome. Several small studies failed to demonstrate a correlation between *CYP2D6* genotype and the risk for side effects. The CPIC suggests that CYP2D6 UM patients forego the use of fluoxetine for another SSRI that relies less on CYP2D6, while CYP2D6 PM patients lower the dosing to 30% to 50% for fluoxetine and observe closely for adverse effects

(Clinical Pharmacogenetics Implementation Consortium (CPIC 2020)).

A case report applying [123I]β-CIT SPECT compared SERT binding in a subject with MDD and comorbid bulimia chronically receiving fluoxetine at 60 mg daily to a set of healthy controls and estimated an occupancy in the thalamic-hypothalamic region of 41%. Given the binding of [123I]β-CIT SPECT to DAT (Laruelle et al. 1994), this is presumably an underestimate although it empirically demonstrated brain penetration of fluoxetine. Applying [11C]DASB PET, in a within-subject design, SERT BP$_{ND}$ was measured before and after 4 weeks of fluoxetine treatment in 18 subjects (Meyer et al. 2004). A 76% occupancy was reported in striatum with similar occupancies across the prefrontal cortex, anterior cingulate cortex, thalamus and midbrain after treatment with the minimum therapeutic dose of 20 mg/day. The study included occupancy assessment from doses of 1 mg to 60 mg daily; a nonlinear plot was fitted to the striatal occupancy to plasma concentration relationship, indicating an ED50 of 2.7 mg/day and an EC50 of 14.8 ng/mL with considerable plateauing of occupancy at plasma concentrations above 75 ng/mL, although a theoretical maximum occupancy of 92% was suggested by the fitting.

There has been some interest in the effects of fluoxetine on dopaminergic pathways, due to evidence of interactions between serotonin and dopamine in animal models and interactions between 5-HT$_{2C}$ receptors and dopamine release in mesocortical and nigrostriatal pathways (Alex et al. 2005). While fluoxetine primarily binds to the SERT with nanomolar affinity, it has some modest inhibition of 5-HT$_{2C}$ receptors albeit at much lower affinity (Tatsumi et al. 1997). The family of D$_2$ receptors may upregulate or downregulate in response to chronic changes in dopamine. An increase of striatal dopamine D2/D3 receptors was shown after treatment of MDD with an SSRI (2 and 13 patients received fluoxetine and paroxetine, respectively) (Klimke et al. 1999). However, a randomised trial comparing fluoxetine and psychotherapy showed thereafter that four months of treatment did not significantly change striatal D$_2$/D$_3$ receptor binding in either group (Hirvonen et al. 2011).

In sum, fluoxetine given at the minimal ED$_{50}$ 20 mg/day for at least 4 weeks yields approximately an 80% SERT occupancy (Meyer et al. 2004). There is a paucity of SERT occupancy data available for single-dose and short-term treatment of fluoxetine. Similar to citalopram, the difference in occupancy between minimum therapeutic doses and high doses is small and

might explain the lack of substantial differentiation among these doses in a clinical trial (Wernicke et al. 1988; Meyer et al. 2004; Jakubovski et al. 2016; Furukawa et al. 2019).

2.2.3. Fluvoxamine

Fluvoxamine, in addition to its primary SSRI activity, has the highest affinity for the sigma 1 receptor, which may account for supposed superior efficacy in psychotic depression (Niitsu et al. 2012). Fluvoxamine has minimal or no interaction with the NET or with muscarinergic or histaminergic receptors. Fluvoxamine is well absorbed after oral intake and protein binding is moderate (77%) and considered to be the lowest among the SSRIs. Fluvoxamine is metabolised to the major and inactive 5-demethoxylated carboxylic acid metabolite via CYP2D6 and to a lesser extent by CYP1A2 (Hemeryck and Belpaire 2002; Miura and Ohkubo 2007), resulting in two metabolites without significant pharmacological activity. Fluvoxamine is a strong inhibitor of CYP1A2, a moderate inhibitor of CYP2C19 and CYP3A4 and a weak inhibitor of CYP2D6 (Preskorn SH 1997; Zhou 2009). Mean t$_{1/2}$ is 15 h (range 9 to 28 h) (van Harten 1995).

Fluvoxamine displays linear pharmacokinetics after single-dose administration throughout the therapeutic range and nonlinear pharmacokinetics at steady state, with disproportionately higher plasma concentrations at higher doses (Perucca et al. 1994). The AGNP level of recommendation to use TDM for fluvoxamine is 2 with a therapeutic reference range of 60–230 ng/mL (Hiemke et al. 2018). Special groups of patients (e.g. the elderly and those with renal insufficiency) do not show much altered pharmacokinetics of fluvoxamine except for patients with liver disease. A dose adaptation for patients with liver impairment is, however, not explicitly mentioned in the summary of product characteristics.

Sparse results from a very low number of small studies indicate that the CYP2D6 genotype has only a very limited effect on fluvoxamine clearance as compared to CYP1A2. Based on weak evidence regarding clinical outcome, Kirchheiner et al. suggested doses of 120% of a standard dose for CYP2D6 homozygous EMs as compared to 90% for heterozygous EMs and 60% for PMs (Kirchheiner et al. 2001). The CPIC did not find sufficient evidence to give dosing recommendations for UMs and fail to see a need for adjustments of dosing in IMs while a 30% dose reduction is suggested for PMs (Hicks et al. 2015).

The first molecular imaging study of fluvoxamine was done in 14 controls to study the acute effects of

low, single doses (12.5–50 mg/day), using [^{11}C]McN5652 PET (Suhara et al. 2003). Thalamic SERT occupancy ranged from $8 - 88\%$ and could be modelled as a nonlinear function of the dose or plasma concentration. Together with data from four MDD-patients treated with fluvoxamine (100–400 mg/day for 3–26 weeks), resulting in SERT occupancies ranging between 77 and 94%, the authors concluded that at least 50 mg/day fluvoxamine is needed to achieve the 80% SERT occupancy threshold observed with other SSRIs (Meyer, Wilson, et al. 2001; Meyer et al. 2004) at minimum clinical doses. A second study was performed with six male healthy subjects measuring [^{11}C]DASB PET SERT-occupancy by fluvoxamine 50 mg/day in a single dose (Takano, Suhara, et al. 2006). This dose yielded SERT occupancies of $72 \pm 4\%$, $72 \pm 13\%$, $71 \pm 2\%$, $75 \pm 9\%$, $76 \pm 3\%$ in the thalamus, amygdala, striatum, prefrontal cortex and hippocampus, respectively.

In summary, fluvoxamine administered at the minimal ED_{50} 50 mg/day for at least three weeks yields approximately 80% SERT occupancy. SERT occupancy was modestly lower after a single dose. The effects of higher fluvoxamine doses on SERT occupancy were hardly investigated, although it could be argued that there is a sufficient number of alternative antidepressants for clinicians for which higher occupancy has been investigated.

2.2.4. Paroxetine

Paroxetine is the most potent blocking agent of the SERT in the brain in the class of SSRI antidepressants. In addition, paroxetine also depicts the highest affinity for the NET and the highest affinity for muscarinergic receptors, which may lead to anticholinergic side effects at higher doses in EMs and at low doses in PMs (Sanchez and Hyttel 1999). Paroxetine exhibits non-linear pharmacokinetics, due to the inhibition of its own metabolism by a metabolite which is irreversibly bound to CYP2D6 (mechanism-based inhibition) resulting in CYP2D6 inactivation (Bertelsen et al. 2003). Paroxetine is thus the most potent inhibitor of CYP2D6 among all SSRIs (Nemeroff et al. 1996), with high potential for drug interactions. In addition, because paroxetine is highly (95%) protein bound, as for fluoxetine and sertraline, caution is also advised during concomitant administration of other highly bound drugs (warfarin, digitoxin) (Kaye et al. 1989). Extensive metabolism via CYP2D6 and CYP3A4 occurs in the liver, and the resulting metabolites do not contribute to the overall pharmacological effect. Mean $t_{1/2}$ is around 24 h with considerable interindividual

variability (6 to 71 h). Recent data support lower paroxetine serum concentrations to be more favourable in depressed patients (Gilles et al. 2005), but the relationship between paroxetine plasma concentrations and its clinical effect is controversial (Tasker et al. 1989; Eggart et al. 2011). The AGNP level of TDM recommendation is 3, with a therapeutic reference range of 20–65 ng/mL (Hiemke et al. 2018), in agreement with data proposing a therapeutic reference range of 20–60 ng/mL based on paroxetine doses of 10–40 mg/day for 6 weeks (Tomita et al. 2014).

Sindrup et al. (Sindrup, Brøsen, Gram 1992; Sindrup, Brøsen, Gram, et al. 1992) showed a correlation between sparteine metabolic ratio, a measure of CYP2D6 activity, and plasma concentrations of paroxetine. The difference between PMs and EMs of CYP2D6 in AUC was 7-fold after a single dose, but only 1.7-fold at steady state, consistent with the non-linear kinetics of paroxetine. A 3.4-fold higher plasma concentration has been reported in PM ($n = 6$) compared to EM ($n = 30$) depressed patients at a daily dose of 20 mg/day (Charlier et al. 2003). One UM subject had undetectable concentrations. In contrast, a modest 1.3-fold difference in steady state plasma concentrations was found between IM and EM depressed patients treated with 20–30 mg/day (Gex-Fabry et al. 2008). Two patients classified as PMs had plasma concentrations within the range found in EMs, while 3 out of 4 UM patients had concentrations below the level of detection. None of the PMs or UMs showed a persistent response to paroxetine. Two further cases of UM patients having repeatedly very low or undetectable plasma concentrations and lack of antidepressant effect have been described (Guzey and Spigset 2006). A dose escalation study in 62 children and adolescents (aged 7–17) found a relationship between CYP2D6 genotype and steady-state weight-normalised apparent oral clearance of paroxetine at a daily dose of 10 mg but not at higher doses (Findling et al. 2006).

Several studies have also shown differences in paroxetine plasma levels in relation to the CYP2D6*10 allele associated with decreased enzyme activity in the Asian population, after single doses (Yoon et al. 2000) and at steady state (Sawamura et al. 2004; Ueda et al. 2006). A 2-fold higher concentration has been found in patients carrying at least one *10 allele compared to those with no *10 allele at a 10 mg daily dose, but not at higher doses (20–40 mg/day). On the other hand, a less than 2-fold difference in paroxetine steady-state concentrations was found between patients with one and those with two functional CYP2D6 alleles, at the daily dose of 30 mg/day, but not

at lower doses (10–20 mg/day) (Ueda et al. 2006), Patients with two decreased function alleles (*10 or *41) had lower steady-state concentrations than patients with only one decreased function allele. This unexpected finding is possibly related to the inhibitory effect of paroxetine on CYP2D6, which is greater in subjects with one functional CYP2D6 allele compared to those with either two or no functional alleles. It has to be noted that the number of functional variants of the CYP2D6 gene analysed varies between studies, as does the definition used for it (e.g. the IM genotype), rendering direct comparison difficult.

The CPIC recommends a 50% reduced starting dose, followed by titration to response, in PMs of CYP2D6, if paroxetine is warranted (Hicks et al. 2013). No dose adjustment of starting dose in other CYP2D6 genotypes/predicted phenotypes is recommended. In UMs, choice of an alternative drug not predominantly metabolised by CYP2D6 is recommended. The DPWG do not give dose recommendations for PMs, while for UMs, an alternative drug is suggested(Annotation of DPWG Guideline for paroxetine and CYP2D6 2018).

Paroxetine has been relatively well investigated with molecular imaging both in healthy controls and in depressed patients. [^{11}C]DASB PET was applied across two studies in a within-subject design, which quantitated SERT BP_{ND} before and after four weeks of paroxetine treatment in 14 subjects (Meyer, Wilson, et al. 2001; Meyer et al. 2004). An occupancy of $85 \pm 6\%$ (SD) was reported in striatum with fairly similar occupancies across other regions (prefrontal cortex $80 \pm 18\%$, anterior cingulate cortex 76 ± 15, thalamus 75 ± 16 and 94 ± 8 in the midbrain) after treatment with the minimum therapeutic dose of 20 mg/day. The study included occupancy assessment for doses from 5 mg to 60 mg daily and a nonlinear plot was fitted for the relationship between striatal occupancy and plasma concentration, indicating an ED_{50} of 5.0 mg/day and an EC_{50} of 2.7 ng/mL with considerable plateauing of occupancy at plasma concentrations above 50 ng/mL although a theoretical maximum occupancy of 93% was suggested by the fitting. Another study reported a similar finding with striatal and thalamic occupancies of $75 \pm 7\%$ and $81 \pm 6\%$ respectively, using [^{11}C]McN 5652 PET in 5 patients treated with 20 to 40 mg daily for 3 to 6 months (Kent et al. 2002). SERT occupancy is somewhat reduced when assessed with the [^{123}I]-ADAM SPECT technique. 10 MDD-patients were treated for 4–6 weeks with paroxetine 20 mg/day and SERT occupancies of 66.4%, 63.0% and 61.3% in the midbrain, thalamus and striatum, respectively, were reported (Catafau et al. 2006).

The increase of SERT occupancy by higher doses was investigated in a randomised, placebo-controlled dose-escalation study (Ruhe, Booij, Weert, et al. 2009). This study showed that increasing the dose of paroxetine to 50 mg/day did not increase response rates, nor improve changes in the HDRS scores. Moreover, SERT occupancy at 6 weeks of paroxetine 20 mg/day (midbrain: 71%; thalamus: 61%) did not increase more after true dose-escalation (midbrain: +1.6%; thalamus: +1.9%) relative to the placebo dose-escalation (midbrain: +3.1%; thalamus: −5.8%). This study thus provided a rationale for the observed flat dose-response relationship for SSRIs (Corruble and Guelfi 2000; Adli et al. 2005; Ruhe et al. 2006; Furukawa et al. 2019). In the same cohort, this group showed an association between SERT occupancy by paroxetine 20 mg/day and a decrease in HDRS scores, but only in carriers of the L_A/L_A SERT promotor polymorphism. In those subjects, higher occupancy was associated with a larger decrease in HDRS scores (Ruhe, Ooteman, et al. 2009).

The effect of SSRIs on 5-HT$_{2A}$ receptors is of considerable interest since 5-HT$_{2A}$ receptors influence calcium-dependent protein kinases and 5-HT$_{2A}$ agonists have euphoriant effects (Vaidya et al. 1997). In a separate cohort, 19 MDD patients and 19 age-matched controls were investigated (Meyer, Kapur, et al. 2001). The patients were treated for six weeks with paroxetine 20 mg/day and, in a within-subject design, changes in 5-HT$_{2A}$ receptor binding with [^{18}F]setoperone PET were assessed in all cortical regions (medial frontal gyrus (BA 9), lateral orbitofrontal cortex, parahippocampal gyrus, posteromedial temporal gyrus and rostral anterior cingulate). Subjects aged 20 to 30 years ($n = 9$) had a 10% decrease in 5-HT$_{2A}$ binding potential after treatment, whereas subjects aged 30 to 40 ($n = 10$) had no change. A significant age by treatment interaction was observed for 5-HT$_{2A}$ binding in all cortical regions. 5-HT$_{2A}$ receptors are largely found in pyramidal cell neurons, which decline with age, and 5-HT$_{2A}$ binding declines with age, hence the best sensitivity of this technique was to detect effects of paroxetine in younger subjects aged 20 to 30. However, the interpretation of these findings is complicated, because with a single PET scan it cannot be distinguished whether changes in binding (BP_{ND}) reflect true changes in receptor density (Bmax) or changes in receptor availability due to competition between radiotracer and endogenous neurotransmitter).

In sum, paroxetine given at the minimal ED_{50} 20 mg/day for at least 4 weeks yields approximately 80% SERT occupancy. SERT occupancy appears to be lower when paroxetine is administered in a single

dose or for short-term treatment. Second, SPECT-based studies with [^{123}I]β-CIT and [^{123}I]-ADAM reported generally lower SERT occupancies than by PET. Finally, higher paroxetine doses, compared to lower therapeutic doses, have modest effects on SERT occupancy and may account for the lack of increasing the clinical effect by raising paroxetine above 20 mg daily. Given the effect of paroxetine on 5-HT$_{2A}$ BP$_{ND}$ with [^{18}F]setoperone PET, it is plausible that 5-HT$_{2A}$ agonist PET radiotracers will be sensitive to paroxetine in future studies.

2.2.5. Sertraline

Sertraline is an SSRI with additional weak dopamine and noradrenaline reuptake inhibition, the latter of no clinical relevance. Sertraline undergoes slow absorption after oral administration and is extensively metabolised in the liver, mainly by N-demethylation to N-desmethylsertraline by CYP2C19 and CYP2B6 which probably are the primary metabolising enzymes (Wang JH et al. 2001; Obach et al. 2005), with CYP2C9, CYP3A4, and CYP2D6 also contributing (Kobayashi K et al. 1999). Sertraline has linear kinetics in the 50–200 mg/day dose range (Doogan and Caillard 1988). The t$^1/_2$ for sertraline is approximately 35 h and about 100 h for desmethylsertraline in most patients except younger men, where it is noticeably shorter (Ronfeld et al. 1997). The plasma concentration of desmethylsertraline is about 1.5 to two times the levels of sertraline (Reis et al. 2009). However, in concentration-equivalent terms, desmethylsertraline is believed to retain less than 10% of the 5-HT reuptake inhibiting capacity compared to sertraline (Owens et al. 1997). The AGNP level of TDM recommendation is 2 with a therapeutic reference range of 10–150 ng/mL (Hiemke et al. 2018). No dose adjustment is necessary in patients with renal impairment (MacQueen et al. 2001) but should be considered in patients with terminal hepatic impairment in whom the t$_{1/2}$ and the AUC are increased. Sertraline minimally inhibits CYP enzymes, resulting in few drug-drug interactions (DeVane et al. 2002) but patient demographics, particularly age, sex and possibly CYP2B6 activity, may influence the pharmacokinetic properties of sertraline (Ronfeld et al. 1997; Axelson et al. 2002; Baumann et al. 2006).

Polymorphisms across the *CYP2C19* and *CYPB6* genes appear to be significantly associated with variability in the metabolism of sertraline (Wang JH et al. 2001; Yuce-Artun et al. 2016; Saiz-Rodríguez et al. 2018). The pharmacogenetic literature of sertraline has been reviewed by the CPIC (Hicks et al. 2015). For CYP2C19 PMs, a dose reduction of 50% was

recommended. For CYP2C19 UMs, data were insufficient to provide recommendations; however, starting with or switching to other SSRIs might be beneficial for these individuals (Hicks et al. 2015).

[^{11}C]DASB PET was applied in a within-subject design and measured SERT BP$_{ND}$ before and after four weeks of sertraline treatment in 14 patients (Meyer et al. 2004). After treatment with the minimum therapeutic dose of 50 to 100 mg daily, this study reported an occupancy of 85 ± 7% (SD) in the striatum, with similar occupancies across the prefrontal cortex (91 ± 16%), anterior cingulate cortex (95 ± 19%), thalamus (77 ± 4%) and midbrain (92 ± 4%). Because this study also included occupancy assessments of doses in the range between 5 mg and 200 mg daily, a non-linear plot was fitted to the striatal occupancy - plasma concentration relationship, indicating an ED$_{50}$ of 9.1 mg/day and an EC$_{50}$ of 1.1 ng/mL with considerable plateauing of occupancy at plasma concentrations above 20 ng/mL although a theoretical maximum occupancy of 88% was suggested by the fitting. Consistent with the issue of reaching a plateau, the same group reported a striatal SERT occupancy of 86 ± 2.0% in four MDD patients who received sertraline 150–200 mg/day for at least 4 weeks compared to controls in a between-subject design (Voineskos et al. 2007). Unexpectedly, in a within-subject design of 4–6 days of sertraline treatment at dosages from 25 to 100 mg/day in 17 healthy subjects, very high occupancy ranging from 130% to 80% across regions of interest was reported with an average value of 107%, suggesting that early occupancy values from sertraline are elevated, in contrast to the acute studies of citalopram and escitalopram occupancy for which initial occupancy values are lower than after longer term treatment (Parsey et al. 2006).

In summary, sertraline given at the minimal ED$_{50}$ 50 mg/day for at least 4 weeks yields approximately 80% SERT occupancy. Early occupancy values in short-term treatment (4 to 6 days) appear quite elevated. Finally, as observed with other SSRIs, the effects of higher sertraline doses on SERT occupancy levels are small and may account for the lack of clinical differentiation of higher doses.

2.3. SNRI

2.3.1. Duloxetine

Duloxetine is a balanced SNRI approved for the treatment of depression and generalised anxiety disorder but also diabetic neuropathic pain, and fibromyalgia (Frampton and Plosker 2007; Carter and McCormack

2009). Duloxetine has a low affinity for other neurotransmitter receptors including alpha$_1$- and alpha$_2$-adrenergic, dopamine D$_2$, histaminergic H$_1$ and muscarinic receptors. Duloxetine is rapidly absorbed following oral administration and the peak plasma concentration occurs approximately 6 h after dosing (Lantz et al. 2003). The absolute oral bioavailability is about 50% (Lantz et al. 2003). Duloxetine is extensively metabolised in the liver primarily by CYP1A2 and, to a lesser extent, by CYP2D6, and by *Phase II* enzymes UDP glucuronyl-transferase (UGT), catechol-O-methyltransferase (COMT) and sulfotransferase (SULT) to form various oxidative and conjugated metabolites (mainly glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy-6-methoxy duloxetine), which are inactive and excreted mainly in the urine (Lantz et al. 2003; Knadler et al. 2011). The t$_{1/2}$ of duloxetine is approximately 12 h (range 8–17 h) (Lantz et al. 2003).

Two studies have suggested that TDM can be regarded as a useful option for guiding duloxetine treatment. One study retrospectively investigated the relationship between serum concentrations of duloxetine from a TDM survey and clinical effects in 103 depressed inpatients (Waldschmitt et al. 2009). Patients treated with duloxetine monotherapy who were very much improved according to clinical global impressions (CGI) had significantly ($p < 0.05$) higher serum levels than patients with moderate, minimal or no improvement (93 ± 53 ng/mL and 47 ± 39 ng/mL, respectively). Duloxetine doses were similar in the two groups (76 ± 27 vs. 83 ± 27 mg/day), both higher than the 60 mg daily dose above which the drug information provided by the company states that no therapeutic advantages can be shown, which suggests the usefulness of performing TDM. Receiver operating characteristics (ROC) curve analysis documented significant predictive properties of duloxetine serum levels ($p = 0.011$) for improvement with a lower threshold concentration of duloxetine of 58 ng/mL (Waldschmitt et al. 2009; Volonteri et al. 2010). A naturalistic, open-label study investigated the correlation between plasma concentrations of duloxetine and clinical outcome and tolerability in 45 outpatients with MDD treated with duloxetine at doses of 30–120 mg/day for 12 weeks (Volonteri et al. 2010). There was a significant curvilinear quadratic relationship between the percentage improvement in Hamilton Rating Scales for Anxiety and steady-state duloxetine concentration ($R^2 = 0.27$; $p = 0.02$) with an optimal anxiolytic effect at plasma concentrations between 40 and 100 ng/mL. On the other hand, no association was found between

HAMD and plasma duloxetine levels ($R^2 = 0.05$; $p = 0.502$), while the occurrence of anxiety or irritability was associated with the highest plasma levels of duloxetine. The AGNP level of TDM recommendation is 2 with a therapeutic reference range of 30–120 ng/mL for duloxetine (Hiemke et al. 2018), which was confirmed in a recent study (de Donatis et al. 2019).

Although *CYP2D6, CYP1A2* and *COMT* polymorphisms might potentially modulate the pharmacokinetics of duloxetine (Beatty et al. 2013), thus far no studies have investigated their associations with the pharmacokinetics of duloxetine and dose recommendations for different *CYP2D6, CYP1A2* and *COMT* genotypes/phenotypes are not possible. Associations between polymorphisms of pharmacodynamic genes and response to treatment have been shown; however, such studies need further validation through replication studies. A significant association between changes in the 17-item HDRS treatment with open-label duloxetine (60–120 mg/day) in Caucasian patients with MDD was found for a carrier of a composite genetic marker (based on *SLC6A2* rs5569 *[G1287A]* AA, *HTR1A* rs6295 *[C(−1019)G]* GG, and *COMT* rs174697 AA/AG) (Houston et al. 2012). Additionally, in the same population, a single-nucleotide and a diplotype containing *COMT* rs165599 and *COMT* rs165737 were associated with HDRS-17 total score changes (Houston et al. 2011). Associations between 825 SNPs in 61 candidate genes and the duloxetine response with change in Hamilton Anxiety Scale scores were examined with set-based testing. Variants in *corticotropin-releasing hormone receptor 1 (CRHR1), dopamine receptor D3 (DRD3), nuclear receptor subfamily group C, member 1 (NR3C1)* and *phosphodiesterase 1 A (PDE1A)* were associated with response in generalised anxiety disorder (GAD). However, only rs4792888 in *CRHR1* showed modest evidence of association with response in major depressive disorder (Perlis et al. 2013). Furthermore, the polymorphisms in *PDE1C, PDE6A, PDE11A, ABCB1* (encoding for PGP), *GRIK4, SLC6A4* or *5-HTT (SERT* gene), and *OPRM1* genes showed no statistically significant associations ($p > 0.05$) with duloxetine treatment response (Perlis et al. 2010).

Occupancies of the SERT of 80% (mean 82 ± 4%, under a single-dose of 60 mg duloxetine; mean 84 ± 3%, under a repeated dose of 60 mg for seven days) were reported in a PET study of healthy subjects using [^{11}C]DASB (Takano, Suzuki, et al. 2006). The occupancies remained reasonably high 72 h after the last administration (47 ± 4%). In another PET study of healthy subjects, using [^{11}C]DASB, occupancies of 68–78% were shown at 20 mg single-doses and

occupancies of 84% at 20 mg administered over a time period of four days. Plasma levels were on average 19.7 ng/mL with a range of 6 to 34 ng/mL (Abanades et al. 2011) ED_{50} and EC_{50} values were not reported in either study. It can be concluded from these studies that SERT occupancy is very high at the clinically-used dose range of 60–120 mg/day.

NET occupancy was measured in eight healthy subjects after a single oral dose using PET and the radioligand (S,S)-[^{18}F]FMeNER-D$_2$, reporting 30% to 40% NET occupancies by the administration of 20 mg to 60 mg of duloxetine (Moriguchi et al. 2017). From their data, the authors calculated an ED_{50} of 77 mg and an EC_{50} of 58 ng/mL for the NET. The study suggests that NET occupancy is somewhat lower than occupancy of the SERT at the recommended doses. There are no NET occupancy studies in steady state during continuous treatment in patients and the question on whether occupancy of the NET contributes to the antidepressant effects of duloxetine remains open.

2.3.2. Venlafaxine

Venlafaxine is composed of a racemic mixture of two pharmacologically active enantiomers: S-(+)-venlafaxine, mainly a serotonin reuptake inhibitor, and R-(-)-venlafaxine, an SNRI. At low doses venlafaxine inhibits mainly the reuptake of serotonin, whereas at higher doses ($\geq$150 mg/day) it inhibits the reuptake of serotonin and noradrenaline. Venlafaxine has no significant affinity for α_1-adrenergic, muscarinic cholinergic and H$_1$ histaminergic receptors. Venlafaxine is available in immediate-release (IR) and extended-release (ER) formulations (Magalhaes et al. 2014).

The peak plasma concentrations of venlafaxine and its main metabolite O-desmethylvenlafaxine are reached after 2 h and 3 h with the immediate release (IR) form, respectively, and after 5.5 h and 9 h with the extended release (ER) form, respectively. Venlafaxine is extensively absorbed from the gastrointestinal tract, but the bioavailability is only about 45% due to extensive first-pass metabolism. Venlafaxine is mainly metabolised in the liver by CYP2D6 to form the active metabolite O-desmethylvenlafaxine, which has been commercialised under the name desvenlafaxine (see further down in the review). The plasma concentration of this metabolite is usually two- to three-fold higher than that of the parent compound. Both venlafaxine and O-desmethylvenlafaxine are metabolised to N-desmethylmetabolites at least partially by CYP3A4 and CYP2C19. The metabolites are primarily excreted by the kidneys in glucuronide conjugated or in unconjugated forms. The $t_{1/2}$ for venlafaxine and O-desmethylvenlafaxine are approximately 5 h and 11 h with the IR form, respectively (Magalhaes et al. 2014). With the ER form, the rate of absorption of venlafaxine is slower than its elimination rate. Therefore, the apparent $t_{1/2}$ of venlafaxine of 15 ± 6 h actually represents the absorption half-life instead of the true disposition half-life (Government of Canada, Drug Product Database online. Product monograph venlafaxine XR, extended release capsules. 2012). The clearance of venlafaxine is reduced in cases of hepatic and renal dysfunction and dose adjustments are recommended. Venlafaxine and its metabolites are PGP substrates, which can influence their absorption, distribution to the brain and elimination (Magalhaes et al. 2014).

Only a limited number of studies including a small number of patients have evaluated the relationship between venlafaxine and O-desmethylvenlafaxine plasma concentrations and antidepressant response, with little concordance. In a study including 76 patients with MDD receiving venlafaxine once a day for 3 to 6 weeks (dose range 37.5 to 375 mg/day), the mean $\pm$ SD plasma levels of the sum of venlafaxine plus O-desmethylvenlafaxine, measured before the morning dose, was higher for responders (198 $\pm$ 80 ng/mL) compared to nonresponders (149 $\pm$ 65 ng/mL). Based on these results, the authors have suggested a target concentration ranging from 125–400 ng/mL for the sum of venlafaxine plus O-desmethylvenlafaxine (Charlier et al. 2002). In another 7-week open-label study including 28 patients with major depressive episode receiving venlafaxine 255 mg/day divided into three doses, the mean $\pm$ SD levels of the sum of venlafaxine plus O-desmethylvenlafaxine, measured before the morning dose, were significantly lower for the responders (239 $\pm$ 24 ng/mL) compared to the nonresponders (406 $\pm$ 172 ng/mL). These results suggest that nonresponse also may be a result of overdosing venlafaxine. Another explanation highlights the methodological problem that inclusion of nonresponders and a flexible dose regimen artificially insinuates that low concentrations of antidepressant drugs are better than high ones (Hiemke 2019). A target therapeutic concentration ranging from 195–400 ng/mL for the sum of venlafaxine plus O-desmethylvenlafaxine was suggested by the authors (Veefkind et al. 2000). In a 4-week study including 35 depressed patients receiving venlafaxine 300 mg/day divided in two doses, a comparison of patients with and without persistent response did not reveal any significant difference for venlafaxine plus O-desmethylvenlafaxine plasma levels at trough. In patients with persistent response

($n = 19$), early response (observed before 2 weeks) was associated with significantly higher venlafaxine $+$ O-desmethylvenlafaxine concentrations than was delayed response (median 725 ng/mL versus 554 ng/mL) (Gex-Fabry et al. 2004). The AGNP level of TDM recommendation is 2 with a therapeutic reference range of 100–400 ng/mL for the sum of venlafaxine and O-desmethylvenlafaxine (Hiemke et al. 2018).

CYP2D6 genotype clearly influences the disposition of venlafaxine and it has been shown that the ratio between venlafaxine and O-desmethylvenlafaxine increases with decreasing enzyme activity from UM to PM. As a consequence, PMs also show higher concentrations of N-desmethylvenlafaxine resulting from the use of an alternative pathway via other cytochromes (Sangkuhl et al. 2014). A possible influence of CYP2C19 genotypes on venlafaxine metabolism has also been suggested, in particular in CYP2D6 PMs or IMs (McAlpine et al. 2011). Currently, only a few studies have investigated the impact of CYP2D6 genetic variation on both response to therapy and risk of side effects. Despite its clear influence on the pharmacokinetics of venlafaxine and some indications that PMs display a lack of response and unfavourable adverse events, there is currently limited evidence to recommend genotyping due to a low number of studies and in part due to conflicting results with regard to clinical outcome. Therefore, dose recommendations are generally not provided for CYP2D6 PMs and IMs but an alternative drug may be chosen to lower the risk of side effects. On the other hand, UMs may receive up to 150% of a standard dose (Samer et al. 2013).

In a sample including 350 adults age 60 or older depressed patients, noradrenaline transporter variants was found to be significantly associated with remission (OR: 1.66; 95%CI: 1.13–2.42)(Marshe et al. 2017). Other genes studied under venlafaxine therapy, without conclusive results so far, are for instance COMT, brain derived neurotrophic factor (BDNF), FK506 binding protein 5 (FKBP5), the DAT (SLC6A3) and the serotonin receptor 2 A (HTR2A). Further studies regarding the stereoselectivity of CYP2D6 and the consequences for the mechanism of action of these enantiomers may aid in understanding the impact of genetic variance on the outcome of venlafaxine therapy.

In a [^{11}C]DASB PET within-subject study, measuring SERT BP_{ND} before and after four weeks of venlafaxine (ER formulation) treatment at the minimum therapeutic dose of 75 mg daily in 18 subjects, an occupancy of $84 \pm 2\%$ (SD) was reported in striatum with similar occupancies across the prefrontal cortex ($91 \pm 11\%$), anterior cingulate cortex ($85 \pm 13\%$), thalamus ($71 \pm 10\%$) and midbrain ($91 \pm 8\%$) after treatment (Meyer et al. 2004). This study included occupancy assessment of doses of 2.5 mg to 225 mg daily. A nonlinear plot was fitted to the striatal occupancy - plasma concentration relationship, indicating an ED_{50} of 5.8 mg/day and an EC_{50} of 3.4 ng/mL with considerable plateauing of occupancy at plasma concentrations above 40–60 ng/mL, although a theoretical maximum occupancy of 92% was suggested by the fitting. However, a limitation of this plasma-occupancy relationship is that the SERT is occupied both by venlafaxine and its active metabolite, O-desmethylvenlafaxine. Since the concentration of O-desmethylvenlafaxine is on average twofold higher than that of the parent compound (Shams et al. 2006), the active moiety (venlafaxine $+$ O-desmethylvenlafaxine) concentration associated with 80% SERT occupancy can be calculated as approximately 60 ng/mL. This value is in line with TDM findings (Reis et al. 2009) which showed that, according to a very large database, treatment with 75 mg venlafaxine daily is associated with a median active moiety concentration of 135 ng/mL (10th percentile 68 ng/mL) (Reis et al. 2009). The highest approved venlafaxine dose (375 mg) is associated with a median concentration of the active moiety of 432 ng/mL (Reis et al. 2009). Thus, the therapeutic reference range recommended by the AGNP ($100 - 400$ ng/mL for active moiety) (Hiemke et al. 2018) is in good agreement with data from this PET study, which documents a SERT occupancy ranging from 80% to 95% at those plasma concentrations. In an additional study with several SSRIs, including 4 MDD patients who received venlafaxine 225–450 mg/day for more than four weeks, a striatal SERT occupancy of $86 \pm 3\%$ was measured with [^{11}C]DASB PET, providing further support for saturation of SERT occupancy by a dose of 150 to 225 mg (Voineskos et al. 2007).

Eight healthy controls treated for nine days with venlafaxine 150 mg/day were investigated with [^{123}I]β-CIT SPECT (Shang et al. 2007). Presumably due to the unblocked specific binding of [^{123}I]β-CIT SPECT to DAT (Laruelle et al. 1994), SERT occupancies were lower, being 53% in the thalamus and 56% in the midbrain.

In sum, venlafaxine given at the minimal ED_{50} of 75 mg/day for at least four weeks yields approximately 80% SERT occupancy. Finally, while there is a step up of approximately 5% in SERT occupancy from the 75 mg dose to 150 mg–225 mg, it would be an interesting future study to look at the effects of higher doses of venlafaxine on NET occupancy. (Rudolph

et al. 1998; Entsuah and Gao 2002). Data on NET occupancy by venlafaxine, however, are not available.

2.3.3. Desvenlafaxine

O-desmethylvenlafaxine, the active metabolite of venlafaxine, has been synthesised and marketed as the racemic desvenlafaxine succinate salt. Similar to venlafaxine, desvenlafaxine is an SNRI and has been approved in the US and some other countries for treatment of MDD at a standard dose of 50 mg/day. Desvenlafaxine has a weak binding affinity for the DAT and, like venlafaxine, it lacks significant activity on muscarinic-cholinergic, H1-histaminergic, or α_1-adrenergic receptors in vitro (Deecher et al. 2006). Desvenlafaxine is metabolised primarily to desvenlafaxine O-glucuronide, N,O-didesmethylvenlafaxine (via CYP3A4) and M9 (a minor metabolite). Desvenlafaxine is primarily eliminated by renal excretion of unchanged drug, and within 72 h of oral dosing approximately 45% of the administered dose is excreted in the urine, 19% as the glucuronide metabolite and less than 5% as N,O-didesmethylvenlafaxine (Nichols et al. 2010; Nichols et al. 2011). Hence, in patients with renal impairment exposure to desvenlafaxine seems to increase with increasing severity and a dose adjustment is recommended in severe renal impairment. The AGNP level of TDM recommendation for desvenlafaxine is 3 with a therapeutic reference range of 100–400 ng/mL (Hiemke et al. 2018). As expected by the fact that desvenlafaxine is the active metabolite of venlafaxine, thus shunting the CYP2D6 metabolism step, and that it is further metabolised by CYP3A and glucuroconjugated, relatively small difference in the pharmacokinetics of desvenlafaxine has been observed between CYP2D6 EMs and PMs, confirming that its metabolism is independent of the CYP2D6 enzyme (Preskorn et al. 2009). From the findings on venlafaxine mentioned above (McAlpine et al. 2011), it may be suggested that CYP2C19 is involved in the N-demethylation of desvenlafaxine to N,O-didesmethylvenlafaxine.

In the occupancy study of venlafaxine, the contribution of venlafaxine versus desvenlafaxine to occupancy could not be separated, since they were highly correlated (Meyer et al. 2004). There are no published occupancy studies of desvenlafaxine in either healthy or psychiatrically ill subjects, which is an unfortunate gap in the literature.

2.3.4. Milnacipran and levomilnacipran

Milnacipran is a selective SNRI with greater inhibition of noradrenaline than serotonin reuptake, approved for the treatment of MDD but also for fibromyalgia in some countries. It has no affinity for alpha-adrenergic, cholinergic or histaminergic receptors (Delini-Stula 2000). Milnacipran is a racemic mixture of the 1S,2R and 1R,2S enantiomers, both of which are active (Deprez et al. 1998). The pharmacokinetics of milnacipran is linear. The oral bioavailability is higher than 85%, and its absorption is not affected by food intake. The peak plasma concentration is reached after around 2 h and binding to plasma proteins is low (approximately 13%). Half-life ($t_{1/2}$) is around 8 h and the drug should therefore be taken twice daily (Delini-Stula 2000). Approximately 50% of the dose is excreted unchanged in urine and 30% as a glucuronide conjugate of the parent drug. Only about 20% undergoes oxidative biotransformation, probably only via CYP3A4 isoform, to form two N-dealkylated and one hydroxylated (p-OH-milnacipran) metabolites. Only the hydroxylated metabolite has pharmacological activity, but it represents only a small amount of the dose (Puozzo et al. 2005). The clearance of milnacipran is significantly prolonged in patients with renal failure; the dose should therefore be adjusted (Delini-Stula 2000). The most common side effects of milnacipran include nausea, vomiting, dizziness, and excessive sweating which may be dose-related (Higuchi et al. 2009; Ruan et al. 2016)

Levomilnacipran (1S,2R-milnacipran) is the more active enantiomer of racemic milnacipran and has been approved for the treatment of MDD. Due to the short $t_{1/2}$ of levomilnacipran, an ER formulation was developed to allow once-daily administration. The maximum plasma concentration is reached after about 6 h and the apparent terminal $t_{1/2}$ is approximately 12 h (Chen, Greenberg, Gommoll, et al. 2015). Renal excretion is the major route of elimination, with approximately 58% of the dose excreted in the urine as unchanged levomilnacipran. Levomilnacipran undergoes desethylation and hydroxylation through CYP3A4 and to a minor extent through CYP2C8, CYP2C19, CYP2D6, and CYP2J2 (Chen, Greenberg, Gommoll, et al. 2015). The main metabolites excreted in urine, which are not pharmacologically active, are N-desethyllevomilnacipran (18% of the dose), levomilnacipran glucuronide (4%) and desethyllevomilnacipran glucuronide (3%). The dose should be reduced in patients with renal impairment (Brunner et al. 2015), a condition which can result in increased plasma levels and prolonged $t_{1/2}$ (Chen, Greenberg, Brand-Schieber, et al. 2015), while remaining generally well-tolerated (Chen et al. 2014). It should also be lowered from the standard 120 mg/day to 80 mg/day or less when

adjunctively used with CYP3A4 inhibitors, which is in contrast to the recommendations for milnacipran. Dose adjustments are not required when levomilnacipran is co-administered with CYP3A4 inducers or drugs metabolised by CYP3A4 (Chen, Boinpally, et al. 2015).

In 12 Han Chinese healthy volunteers receiving the usual dose of 50 mg milnacipran twice daily, the mean ± SD plasma concentration of trough samples was 69 ± 14 ng/mL after 8 days of treatment (Ruan et al. 2016). A study including 49 Japanese patients with MDD receiving milnacipran 50 mg twice daily evaluated the relationship between milnacipran plasma levels at 4 weeks and antidepressant response at 6 weeks. Thirty-four patients (69.4%) were responders ($\geq$ 50% decrease in the baseline MADRS score). The plasma level of milnacipran ranged between 39–157 ng/mL. The mean ± SD plasma milnacipran level, measured approximately 12 h after the last bedtime dose, was similar when comparing responders (82 ± 29 ng/mL) and non-responders (79 ± 23 ng/mL), $p = 0.70$ (Higuchi et al. 2003). The AGNP level of TDM recommendation for milnacipran is 2 with a therapeutic reference range of 100–150 ng/mL (Hiemke et al. 2018). The AGNP level of TDM recommendation for levomilnacipran is 3 with a therapeutic reference range of 80–120 ng/mL based on concentrations that would be expected under therapeutic doses (Hiemke et al. 2018).

Milnacipran does not interact with CYP1A2, CYP2C19, CYP2D6 or CYP3A4 activities (Puozzo et al. 2005). There are no genetic data available investigating UGT enzymes and their effects on milnacipran plasma levels or on therapeutic outcome. No recommendations are available with respect to phase I or phase II enzyme genotypes and milnacipran doses. Polymorphisms in the NET, the α_{2A} adrenergic receptor (rs1800544), the -1019 C/G polymorphism of the 5-HT$_{1A}$ receptor and/or the *BDNF* genes, but not in the *SERT* gene, might contribute to the therapeutic response to milnacipran (Yoshida et al. 2004; Yoshida et al. 2007; Kato et al. 2015). Moreover, the Met/Met genotype of the Val158Met polymorphism of *COMT* (rs4680) was associated with a more rapid response to milnacipran (Yoshida et al. 2008). No pharmacogenetic studies specifically investigating levomilnacipran have been published so far.

A PET study, using [11C]DASB as the radiotracer, revealed that the mean occupancy of the SERT in the thalamus was 33.0% at 50 mg of milnacipran, 38.6% at 100 mg, 60.0% at 150 mg, and 61.5% at 200 mg in six patients with MDD (Nogami et al. 2013). Estimated

ED$_{50}$ was reported to be 122.5 mg and the EC50 was 145.4 ng/mL. Mean occupancy of the NET, measured with (S,S)-[^{18}F]FMeNER-D2, was 25.3% at 25 mg, 40.0% at 100 mg, 47.3% at 125 mg, and 49.9% at 200 mg. The corresponding estimated ED$_{50}$ was 149.9 mg and the EC$_{50}$ was 158.7 ng/mL in another six patients with MDD (Nogami et al. 2013). Thus, occupancy of both the SERT and the NET are relatively low at clinically-used doses. At the plasma levels recommended by the AGNP (50 $-$ 110 ng/mL) (Hiemke et al. 2018), SERT and NET occupancy is supposedly well below 50%. There is no published report on the binding of levomilnacipran to a molecular target in the human or non-human primate brain.

2.4. Others

2.4.1. Agomelatine

Agomelatine is an agonist at melatonin MT$_1$ and MT$_2$ receptors and an antagonist at 5HT$_{2c}$ receptors. The standard dose of agomelatine is 25 mg once a day before sleeping. After two weeks, the dose can be increased to a maximum dose of 50 mg once a day. Agomelatine is well absorbed (>80%) but oral bioavailability is only 5% due to extensive first-pass metabolism in the liver with a large interindividual variability. C$_{max}$ is reached after 1–2 h and t$_{1/2}$ is 1–2 h (Zupancic and Guilleminault 2006; European Medicines Agency: Valdoxan: European public assessment report: Summary of product characteristics 2009; Koesters et al. 2013). Agomelatine is mainly metabolised by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19 and it does not inhibit or induce CYP enzymes. Drug-drug interactions might occur with inhibitors of CYP1A2 (for example, fluvoxamine) and inducers of CYP1A2 (for example, tobacco smoking) (Zupancic and Guilleminault 2006; European Medicines Agency: Valdoxan: European public assessment report: Summary of product characteristics 2009). For example, exposure to agomelatine among smokers was one-third to one-fourth compared to non-smokers, but smoking status was not associated with difference in response in a small study (European Medicines Agency: Valdoxan: European public assessment report: Summary of product characteristics 2009; Englisch et al. 2019). Also, the association of agomelatine with potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin is contraindicated. Agomelatine is associated with an increased risk of liver injury and schedules for liver function tests have been defined before and after a treatment with agomelatine and after a

dose increase (interval of 14 days to one month during the first 6 months) (Voican et al. 2014).

There is no association between the plasma concentration of agomelatine and response. Therefore, TDM is only useful for special indications or problem solving, which is also reflected by the low AGNP level of TDM recommendation (level 4) with a very broad therapeutic reference range of 7 to 300 ng/mL 1–2 h after 50 mg of agomelatine (Hiemke et al. 2018). Of note, because of the very short $t_{1/2}$, it is not possible to measure trough drug concentrations (Hiemke et al. 2018).

Pharmacogenetic data are scarce regarding agomelatine, contained in a few drug interaction studies suggesting a major involvement of CYP1A2 in its metabolism (see above (Song et al. 2014; Saiz-Rodríguez et al. 2019).

There is no published PET study on the binding of agomelatine to a molecular target in the human or non-human primate brain.

2.4.2. Bupropion, hydroxybupropion

Bupropion, a dopamine and noradrenaline reuptake inhibitor (Stahl et al. 2004), is marketed in three different bioequivalent formulations, immediate release (IR), sustained release (SR) and extended release (XR) as an antidepressant, but also for cigarette smoking cessation. C_{max} is reached at 2, 3 and 5 h for the IR, SR and XR formulations, respectively (Jefferson et al. 2005). Bupropion is extensively metabolised by the liver into three active compounds, with hydroxybupropion being the primary active metabolite which is formed by CYP2B6 (Jefferson et al. 2005). Bupropion is chiral and CYP2B6 stereoselective metabolism is observed with (S)-bupropion being metabolised at more than three times the rate of (R)-bupropion (Coles and Kharasch 2008). Because hydroxybupropion has two chiral centres, four enantiomers should be observed: however, only (R,R)-hydroxybupropion and (S,S)-hydroxybupropion are found (Coles and Kharasch 2008). C_{max} of hydroxybupropion is reached 3 h after the administration of bupropion IR, and at steady state, a 17-fold higher AUC than bupropion is observed. Bupropion and hydroxybupropion have a comparable mean $t_{1/2}$ of 20 h in healthy subjects (Full prescribing information for Wellbutrin (revised 11/2019) 1985). In eight patients with severe hepatic cirrhosis, a 3-fold increase of bupropion AUC compared to healthy subjects as well as a $t_{1/2}$ increase of 10 h was observed (Jefferson et al. 2005). Dose and/or frequency of dosing should therefore be reduced in patients with mild hepatic impairment not exceeding

75 mg daily in those with moderate to severe hepatic impairment (Full prescribing information for Wellbutrin (revised 11/2019) 1985). While no changes of bupropion pharmacokinetic parameters were observed in end-stage renal disease patients, AUC and $t_{1/2}$ of hydroxybupropion were increased by 136% and 73%, respectively, compared to healthy patients, suggesting a possible accumulation of the major active metabolite (Coles and Kharasch 2008). A higher bupropion C_{max} was observed in the elderly compared to younger subjects; however, the mean AUC values of bupropion and hydroxybupropion were found to be similar (Jefferson et al. 2005). An open-label study on six elderly patients reported a similar mean $t_{1/2}$ of the two latter components of 34.2 h, which is higher than the above-mentioned $t_{1/2}$ in adult subjects (Full prescribing information for Wellbutrin (revised 11/2019) 1985; Sweet et al. 1995). These results suggest that geriatric populations are possibly at risk of accumulating bupropion and its metabolites and should be carefully monitored.

Co-prescription of the CYP2B6 inhibitors clopidogrel and ticlopidine led to a bupropion AUC increase of 60% and 90%, respectively (Turpeinen et al. 2005). Inversely, co-administration of carbamazepine led to a decrease of 90% in the AUC of bupropion and an increase of 50% in the AUC of hydroxybupropion, suggesting induction of CYP2B6 (Ketter et al. 1995). Bupropion is a CYP2D6 inhibitor and special attention should be paid in patients with concomitant medication. The pharmacokinetics of bupropion and its active metabolites were found to be linear across the 50 to 200 mg dose range. An inverse relationship between bupropion and hydroxybupropion plasma concentration and therapeutic response was reported, whereas the maximum antidepressive response was observed with trough concentrations of bupropion below 100 ng/mL and of hydroxybupropion below 1200 ng/mL (Preskorn 1983; Golden et al. 1988; Preskorn et al. 1990; Goodnick 1992). Inversely, a mean hydroxybupropion concentration of 475 ng/mL was observed in responders, which was significantly higher than in the non-responder group (222 ng/mL) in young patients aged 11 to 17 years (Daviss et al. 2006). Receiver operating characteristic analysis of 52 adult patients found that hydroxybupropion serum concentrations higher than 860 ng/mL should be obtained for an improvement in antidepressive response (Laib et al. 2014). The AGNP level of TDM recommendation for bupropion is 2 with a therapeutic reference range of 850–1500 ng/mL for hydroxybupropion alone (Hiemke et al. 2018).

Although the influence of *CYP2B6* polymorphisms on bupropion PK parameters has been investigated in several clinical studies (Kirchheiner, Klein, et al. 2003; Benowitz et al. 2013; Ilic et al. 2013), very limited data are available on their effects on antidepressant outcome. One study linked the *5-HT₂A* gene polymorphism rs2770296 to remission with bupropion and the dopamine-transporter (DAT) polymorphism rs6347 to response to bupropion (Tiwari et al. 2013)

Bupropion has been shown to inhibit the DAT. However, doubt has been raised concerning this inhibition due to its low affinity to the transporter (Meyer et al. 2002). In a PET study using [¹¹C]RTI-32, an occupancy of 14% of the DAT (confidence interval of 6–22%) was shown in eight MDD patients, when treating them with 100 mg/day for seven days, 200 mg the following seven days, and 300 mg the consecutive seven days (Meyer et al. 2002). Plasma levels were on average 90 ± 40 ng/mL for bupropion and 1107 ± 700 ng/mL for hydroxybupropion (Meyer et al. 2002). Active moiety (bupropion + hydroxybupropion) concentrations of approximately 1200 ng/mL are in good agreement with the therapeutic reference range of 850–1500 ng/mL for hydroxybupropion recommended by the AGNP (Hiemke et al. 2018). Using [¹¹C]-βCIT-FE, another PET study of six healthy subjects showed occupancies of 25.2–26% of the DAT when administering 150 mg daily for three days and 150 mg every twelve hours for another eight days. Mean plasma levels were 106 ng/mL for bupropion and 508 ng/mL for hydroxybupropion (Learned-Coughlin et al. 2003).

In a SPECT study of twelve healthy subjects and nine MDD patients, using TRODAT-1, average occupancies of the DAT of 21 ± 28% were shown in depressed patients, having administered 150 mg bupropion daily for three days, and 300 mg for another four weeks. Mean plasma levels on day seven were 54 ± 25 ng/mL for bupropion and 545 ± 351 ng/mL for hydroxybupropion. On day 15, mean plasma levels of bupropion were 39 ± 19 ng/mL and of hydroxybupriopion 558 ± 321 ng/mL (Argyelan et al. 2005). The relatively low plasma levels suggest that the administered doses of bupropion might have been too low, because hydroxybupropion levels were below the therapeutic reference range suggested by the AGNP.

PET studies in rhesus monkeys using [¹¹C]CIT showed occupancies of 85% of the DAT, when administering doses of 5 mg/kg intravenously (Eriksson et al. 2011). PET studies in rats using [¹¹C]cocaine demonstrated occupancies of the DAT of 35% on average, when administering 11 mg/kg, a dosage equivalent to 150 mg in humans, and 25 mg/kg bupropion intraperitoneally (Egerton et al. 2010). Interestingly, using [¹¹C]raclopride, these researchers did not detect a measurable dopamine release following administration of 150 mg bupropion in human subjects. Another study investigated DAT blockade with radafaxine, the (+)-isomer of hydroxybupropion. In a PET study of eight healthy controls using [¹¹C]cocaine mean occupancies of 20–22% was shown, with maximal occupancies of 30–33% for any one of the caudate, putamen and ventral striatum, when administering 40 mg radafaxine as a single dose. The peak plasma level measured was 89.7 ng/mL (Volkow et al. 2005).

In sum, the available PET studies show that bupropion at clinically-used doses inhibits the DAT to a remarkably low extent. These studies raise the question as to whether this compound exerts its clinical effects through mechanisms other than monoamine reuptake inhibition.

2.4.3. Isocarboxazid

Isocarboxazid is a non-selective and irreversible monoamine oxidase (MAO) inhibitor, causing impaired metabolism and thereby increased brain levels of biogenic amines like serotonin and noradrenaline. Its metabolism is not well characterised; in fact only one human study from 1962 has been published (Koechlin et al. 1962). Using indirect methodology, the authors suggest that two pathways dominate; hydrolysis of the amide bond to benzylhydrazine and 5-methyl-3-isoxazole-carboxylic acid, and oxidative metabolism to benzoic acid. Both benzylhydrazine and benzoic acid are further metabolised to hippuric acid, which is excreted in the urine (Koechlin et al. 1962). The $t_{1/2}$ of isocarboxazid in humans is not known. No studies related to the inter- or intraindividual variability in the metabolism of isocarboxazid have been published. Moreover, there are no published studies attempting to identify dose/plasma concentration relationships or plasma concentration/effect relationships. From a theoretical point of view, a drug acting as an irreversible inhibitor might be less suitable for TDM purposes, but as increasing the dose is considered to increase the therapeutic effect (Shulman et al. 2013), there might be potential for TDM.

No information is available on the enzymes involved in the degradation of isocarboxazid in humans. Regarding the amide cleavage, it has been suggested that an amidase or alternatively an esterase/peptidase is involved (Moroi and Sato 1975) while data with microsomes suggest an involvement of carboxylesterase in monkeys (Moroi and Kuga 1980). Of

note, these studies are old and used non-specific techniques, and as knowledge of enzymes and nomenclature have been evolving during the last decades, the naming used in these studies might be confusing. In addition, it is unknown which of the two suggested metabolic pathways is predominant in humans. Among the reported enzymes, the carboxylesterases *CES1* and *CES2* genes display genetic polymorphisms possibly affecting the metabolism of other drugs (Merali et al. 2014). Regarding the oxidative metabolism of isocarboxazid, nothing is known on the enzyme(s) involved, but the type of reaction suggests the possible implication of CYP enzyme(s).

There are no published reports on the binding of isocarboxazid to molecular targets in the human or non-human primate brain.

2.4.4. Maprotiline

Maprotiline, a tetracyclic antidepressant, is highly selective for noradrenaline reuptake inhibition, and is also a H1 receptor antagonist. The major metabolic pathways of maprotiline are the N-demethylation by CYP2D6 to desmethylmaprotiline and the hydroxylation to 3-hydroxymaprotiline, which are both less active. CYP1A2 has also been shown to be involved in maprotiline demethylation (Brachtendorf et al. 2002). Mean $t_{1/2}$ is 48 h (Brachtendorf et al. 2002).

A relationship between plasma concentrations of maprotiline and therapeutic response (Gaertner et al. 1982; Hrdina and Lapierre 1986) and adverse effects (Kurata et al. 1987; Kasper et al. 1993) has been shown. The AGNP level of TDM recommendation is 2 with a therapeutic reference range of 75–130 ng/mL for maprotiline (Hiemke et al. 2018). Maprotiline serum concentrations are not influenced by renal deficiency while dose adaptations should be performed in cases of liver insufficiency, with TDM recommended.

In an experimental study, C_{max} of maprotiline was 2.7-fold greater and the mean AUC was 3.5 times higher in PMs of debrisoquine, a phenotyping test for and a marker of CYP2D6 activity (Firkusny and Gleiter 1994). According to these data, dose adaptation has been recommended with 40% and 130% of the average dose in PMs and EMs, respectively (Kirchheiner et al. 2001). In more recent pharmacogenetics reviews (Swen et al. 2011; Hicks et al. 2015) maprotiline was not considered. One genetic study assessed seizures and myoclonus adverse events during antidepressant treatment, including reports from the Swedish Adverse Drug Reactions Advisory Committee with 8 patients with such adverse events during maprotiline treatment (Spigset et al. 1997). Of the 3 patients treated with maprotiline who could be genotyped for CYP2D6 and CYP2C19, none was found to be a PM. The authors concluded that concomitant treatment of patients with inhibitors of CYP2D6 is the main risk factor for developing seizures during maprotiline treatment (Spigset et al. 1997).

There is no published report on the binding of maprotiline to a molecular target in the human or non-human primate brain.

2.4.5. Mianserin

Mianserin is a tetracyclic antidepressant with a chemical structure similar to mirtazapine and is also a noradrenergic and serotonergic antidepressant. It is administered as a racemate of its S- and R-enantiomers. S-mianserin is considered the more potent enantiomer (Pinder and van Delft 1983). Mianserin is metabolised mainly by N-demethylation, 8-hydroxylation, N-oxidation and N-glucuronidation (for information on the stereoselective metabolism of mianserin, see the corresponding paragraph). The main metabolite in plasma, desmethylmianserin, is considered to contribute to the pharmacological effects of the drug (Pinder and van Delft 1983). In vitro studies have indicated the major involvement of CYP2D6 in the hydroxylation of mianserin, with stereoselectivity towards the S-enantiomer, while the N-demethylation is largely catalysed by CYP1A2 showing stereoselectivity for the R-enantiomer (Koyama et al. 1996). In vivo, the elimination of both mianserin and desmethylmianserin is dependent on CYP2D6 activity, and highly enantioselective for the S-enantiomer (Dahl et al. 1994). CYP3A4 also has a role, as indicated by in vitro studies (Koyama et al. 1996) and a patient study showing induction of mianserin metabolism by carbamazepine (Eap et al. 1999). The $t_{1/2}$ of mianserin is on average 30 h (range 14–60 h). Higher (on average by 42%) steady-state plasma concentrations per dose in women compared to men (Reis et al. 2009) and a low but significant correlation between age and dose-adjusted plasma concentrations of mianserin (Otani et al. 1993; Reis et al. 2009) have been reported.

There is no convincing evidence for a clear relationship between plasma concentrations of mianserin and response. A therapeutic reference range of 15–70 ng/mL for mianserin (non-enantiomeric assay) has been suggested (Hiemke et al. 2018), based on early concentration-effect studies (Montgomery S et al. 1978) and data on the range of concentrations achieved at therapeutic doses (Montgomery SA et al. 1983; Otani et al. 1993; Mihara, Otani, Tybring, et al. 1997).

In a single dose (30 mg) study in Swedish healthy volunteers phenotyped for CYP2D6 using debrisoquine as a probe drug, a significant correlation between CYP2D6 activity and the AUC of both mianserin and desmethylmianserin was found. The AUCs of mianserin and desmethylmianserin were on average 80% and 50% higher in PMs than in EMs of CYP2D6 (Dahl et al. 1994). The influence of CYP2D6 was limited to the major and more potent S-enantiomer of mianserin. A study in 15 Japanese patients treated with 30 mg of mianserin per day for 3 weeks showed about 2-fold higher plasma concentrations of S-mianserin together with a higher proportion of responders in carriers of the CYP2D6*10 allele compared to those with two functional alleles (Mihara, Otani, Tybring, et al. 1997). The highest S-mianserin concentrations were found in one patient carrying the *10 allele together with *5. No relationship was found between the CYP2D6 genotype and R-mianserin concentrations. In contrast, no significant effect of CYP2D6 genotype on the concentration-to-dose ratios (C/D) of either S- or R-mianserin, or of desmethylmianserin was found in a study in 29 Caucasian patients (21 homozygous EMs, 7 heterozygous EMs and one PM, genotype based on analysis of CYP2D6*3 and *4) treated with mianserin (10–360 mg/day, mean 67 mg/day) (Eap et al. 1998). This study suggested that even though CYP2D6 is involved in the metabolism of mianserin, the genotype has only a moderate influence on the steady-state concentrations of the enantiomers of mianserin. The discrepancies between the studies in Japanese and Caucasian patients could be related to ethnicity, or the doses used, as the contribution of CYPs other than CYP2D6 to the elimination of mianserin might increase at higher drug concentrations. Mianserin is not included either in the DPWG or the CPIC guidelines.

There is no published report on the binding of mianserin to a molecular target in the human or non-human primate brain. The respective PET radiotracer, labelled with carbon-11, has only a limited degree of regional specificity of binding in the living brain (Marthi et al. 2002).

2.4.6. Mirtazapine

Mirtazapine, a tetracyclic noradrenergic and specific serotonergic antidepressant (NaSSA), prescribed as a racemate, has its pharmacological effect mediated by blockade of presynaptic noradrenergic alpha$_2$-autoreceptors and alpha$_2$-heteroreceptors that enhance noradrenaline and serotonin release (de Boer 1996). Furthermore, mirtazapine has a low affinity for 5-HT$_1$ receptors but blocks postsynaptic 5-HT$_2$ and 5-HT$_3$ receptors (de Boer 1996). Mirtazapine is rapidly and well absorbed from the gastrointestinal tract and bioavailability is approximately 50%, with peak plasma concentrations reached within 2 h (Timmer et al. 2000). The main metabolic pathways of mirtazapine are 8-hydroxylation (approximately 40%) catalysed by CYP2D6 and to a lesser extent by CYP1A2, glucuronidation (25%), N-demethylation (25%) and N-oxidation (10%) all catalysed by CYP3A4. The 8-hydroxylated and demethylated metabolites are further conjugated with glucuronic acid and/or sulphuric acid. Due to its lower exposure and lower pharmacological activity, desmethylmirtazapine contributes only to 5 to 10% of the overall activity of mirtazapine. The pharmacokinetics of mirtazapine is dependent on age and gender, females and the elderly showing higher plasma concentrations than males and young adults. The mean t$_{1/2}$ of mirtazapine ranges from 20 to 40 h (mean 25 h) and its active metabolite desmethylmirtazapine has a similar t$_{1/2}$ (Timmer et al. 2000).

Despite a pronounced interindividual variability, a linear relationship was found between mirtazapine plasma concentration and dose in the range of 15 to 80 mg/day, with observed plasma concentrations ranging on average from 5 to 100 ng/mL for therapeutic dosages (15–45 mg/day). Furthermore, mirtazapine appears to have a broad therapeutic index and does not cause serious toxicity even when taken in a substantial overdose. Inhibitors of CYP2D6 and CYP3A4 cause modestly increased mirtazapine plasma concentrations (approximately 17–30%) without leading to clinically relevant consequences, while CYP3A4 induction causes a considerable decrease (approximately 60%) in mirtazapine plasma concentrations. Liver and moderate renal impairment cause an approximately 30% decrease in oral mirtazapine clearance while severe renal impairment causes a 50% decrease in clearance (Timmer et al. 2000).

Responders to mirtazapine treatment presented with higher plasma concentrations than non-responders, revealing a threshold concentration of 30 ng/mL (Grasmader et al. 2005). However, plasma concentration may be of minor relevance for the management of mirtazapine side effects when standard doses are administered. The AGNP level of TDM recommendation for mirtazapine is 2 (Tiwari et al. 2013; Hiemke et al. 2018) with a therapeutic reference range of 30–80 ng/mL (Hiemke et al. 2018).

Although the involvement of CYP2B6 in the metabolism of mirtazapine is unclear, it has been suggested to influence its antidepressant response. Thus, *CYP2B6*6/*6* carriers showed a significantly reduced

HDRS score at the end of a treatment study of 45 patients with mirtazapine for 8 weeks (Jaquenoud Sirot et al. 2012). Moreover, these patients had higher concentrations of the mirtazapine metabolite S-OH-mirtazapine. CYP2D6, CYP2C19, and CYP1A2 did not influence the antidepressant response to mirtazapine (Jaquenoud Sirot et al. 2012). Incidentally, CYP2D6 influences plasma levels of S-mirtazapine and the S-mirtazapine/R-mirtazapine ratio only in non-smokers; in smokers, CYP1A2 probably compensates for CYP2D6 PM status (Lind et al. 2009; Jaquenoud Sirot et al. 2012). CYP2D6 does not influence mirtazapine effects on heart rate or blood pressure (Kirchheiner, Henckel, et al. 2004) and altering mirtazapine dosage between various CYP2D6 genotypes is not recommended (Swen et al. 2011).

An association has been described between the MAO-A-linked polymorphic region with the response to mirtazapine (Tzeng et al. 2009). An association between the MAOA T941G (rs6323) polymorphism and the antidepressant response to mirtazapine (but not to paroxetine) was found in female but not in male patients (Tadic, Muller, et al. 2007). On the other hand, a study of the intronic SNP A644G of MAO-B found a statistically significant pharmacogenetic effect of the antidepressant response in females treated with paroxetine, but not in males or females treated with mirtazapine (Tadic, Rujescu, et al. 2007). Positive findings for the COMT Val/Met polymorphism (rs4680), with poorer antidepressant response to mirtazapine in the Met/Met genotype have not been confirmed (Szegedi et al. 2005).

Serotonergic polymorphisms generally do not influence the antidepressant response to mirtazapine. For the functional G-1438A promoter variation of the 5-HT_{2A} receptor gene (rs6311), an association was found with the sleep-promoting effects of mirtazapine (Kang et al. 2007) but not with the antidepressant response per se (Kang et al. 2007). No consistent associations were found between the antidepressant response to mirtazapine and the serotonin transporter – linked polymorphic region (5-HTTLPR) (Lesch and Mossner 1998; Staeker et al. 2014) or the BDNF Val/Met polymorphism (rs6265) (Kang et al. 2010) or the FKBP5 polymorphism (Sarginson et al. 2010).

A PET study, using [^{11}C]MDL 100,907 as the radiotracer, showed that a single tablet of mirtazapine 30 mg results in a mean of 60% occupancy of 5-HT_{2A} receptors at 90 min post-dose (i.e. expected peak) without significant regional differences (from 27% in the putamen to 70% in the occipital lobe) in this small group of five healthy individuals (Hinz et al. 2007).

Single oral administration of mirtazapine 15 mg led to 80–90% occupancy of histamine H_1 receptors at 1.1 h post-dose, measured with [^{11}C]doxepin, in the cerebral neocortex in five healthy males. H_1 receptor occupancy was found to be correlated with subjective sleepiness at 120 and 180 min after the administration (Sato et al. 2013).

2.4.7. Moclobemide

Moclobemide is a reversible and selective inhibitor of the MAO-A. It increases cerebral dopamine, serotonin and noradrenaline, but its reversible inhibitor properties provide a better safety profile than irreversible MAO inhibitors. Moclobemide is well absorbed from the gastro-intestinal tract, but the absorption is delayed in the presence of food (Raaflaub et al. 1984). Following a single oral dose of between 50 mg and 800 mg, the maximum plasma concentration ranged from 0.25 to 11.2 µg/mL, and was attained in 0.5 to 1.5 h (Mayersohn and Guentert 1995). The mean trough plasma concentration in steady-state conditions was 0.22 µg/mL for a 100 mg daily dose (Schoerlin et al. 1987). Because of the short elimination $t_{1/2}$ it has been recommended, after multiple doses, to measure plasma concentrations taken at 4 and 6 h following intake, since this correlates best with AUC (Ignjatovic et al. 2011). Moclobemide undergoes an extensive hepatic metabolism, mainly via CYP2C19, into mainly inactive metabolites (Gram et al. 1995). Half-life ($t_{1/2}$) ranges from 1 to 2 h (mean 1.5 h) in healthy subjects, but is significantly increased to 3.9 h in patients with hepatic cirrhosis (Stoeckel et al. 1990). After multiple administrations, bioavailability increased and clearance decreased compared to single-dose administration, suggesting possible enzymatic saturation and/or auto inhibition (Mayersohn and Guentert 1995). Moclobemide is an inhibitor of CYP2D6, CYP1A2 and CYP2C19, the inhibition of CYP2C19 supports the auto-inhibition hypothesis (Gram et al. 1995; Härtter et al. 1996). Moclobemide doubles the AUC for omeprazole (also metabolised by CYP2C19) and omeprazole-sulfone (the major metabolite) in CYP2C19 EMs, while moclobemide does not influence the AUC for omeprazole and omeprazole-sulfone in CYP2C19 PMs (Cho et al. 2002). The relationship between plasma concentration and the HDRS scale was investigated in 16 patients treated with a daily dose of 300 mg moclobemide for 28 days. Even when an improvement was observed during treatment, no significant association was observed between plasma concentration and clinical response (Fritze et al. 1989). A post hoc analysis of six pre-

registration and six post-marketing studies found a positive correlation between plasma concentration and side effects (Guentert et al. 1995). The AGNP level of TDM recommendation for moclobemide is 3 with a therapeutic reference range of 300–1000 ng/mL (Hiemke et al. 2018).

In a study of 62 patients, no association was found between the MAO-A – linked polymorphic region (MAO-A-LPR) and the antidepressant response to moclobemide (Muller et al. 2002). The main elimination pathway of moclobemide is a saturable metabolism by CYP2C19 (Gram et al. 1995; Yu KS et al. 2001): in healthy volunteers, inhibition of CYP2C19 by omeprazole in CYP2C19 EMs led to moclobemide pharmacokinetics similar to that found in PMs, while omeprazole inhibition of CYP2C19 did not influence moclobemide pharmacokinetics in PMs (Yu KS et al. 2001). Based on pharmacokinetic data, Kirchheiner et al. recommended a dose reduction by 40–60% in CYP2C19 PMs (Kirchheiner et al. 2001). On the other hand, no change in moclobemide dosage based on metabolizer status has also been recommended (Swen et al. 2011) as there is no evidence of increased prevalence of adverse effects in CYP2C19 PMs. Thus, although it is not advised to change the dosage of moclobemide in CYP2C19 PMs on a routine basis, the prescriber might consider starting with a lower dosage as advised as part of the daily clinical practice. Of note, an association between plasma concentrations of moclobemide and adverse events has been reported but this not was replicated (Guentert et al. 1995).

In healthy volunteers during the modelling of [^{11}C]-harmine for PET, moclobemide had an 80% occupancy across grey matter regions (prefrontal cortex, anterior cingulate cortex, putamen, thalamus, and temporal cortex) after one week of 300 mg bid in healthy volunteers (Ginovart et al. 2006).

Since MAO-A levels are elevated in MDD (Meyer et al. 2006; Meyer et al. 2009; Johnson S et al. 2011), it is important to assess occupancy in patients with major depressive episodes. A study using [^{11}C]harmine PET investigated the treatment of 6 MDD-patients with 6 weeks moclobemide at 300 mg bid (Sacher et al. 2011). Applying the Lassen plot, on average, a 74 ± 6% MAO-A occupancy was found. There was no effect from an herbal intervention, St. Johns Wort 600 mg bid, which has been purported to treat MDD through inhibition of MAO-A on MAO-A V_T (radiotracer binding), nor systematic change in MAO-A V_T during test-retest evaluation of 10 controls was observed. With the same radiotracer, in a six-week treatment study, a clear dose-occupancy relationship was established for moclobemide across 20 major depressive episode subjects for a dosing range of 150 mg bid to 600 mg bid (Chiuccariello et al. 2014). The theoretical maximum occupancy for moclobemide was 88%. Occupancy was 74 ± 8% (SD) after treatment with 150 mg to 300 mg bid, and 84% ± 6% after treatment with 450 to 600 mg bid. Unfortunately, no relationship between plasma level and occupancy was found, presumably due to the rapid $t_{1/2}$ of 1–2 h in plasma. Interestingly, the occupancy of six-week treatment with phenelzine was also assessed in four major depressive episode subjects and was 87 ± 7%, suggesting that high dose moclobemide, a better-tolerated treatment, approaches the MAO-A inhibition of phenelzine at a common treating dosage. While the usual maximum clinical dose of moclobemide is 300 mg bid, higher doses are sometimes used in clinical situations and these higher doses would be expected to result in significantly higher occupancy since the occupancy plateau is not reached until a dose of 450 mg to 600 mg bid. However, it has to be kept in mind that phenelzine is an irreversible MAO inhibitor, while moclobemide blocks the enzyme reversibly. Thus, depending on transmitter concentrations, even at comparable MAO occupancy an irreversible MAO inhibitor might still be more effective in preventing the degradation of monoamines in vivo.

2.4.8. Nefazodone

Nefazodone combines potent blockade of the 5-HT$_{2A}$ receptor with a more modest and reversible effect on serotonin uptake inhibition (Preskorn SH 1995). It is rapidly and completely absorbed but is subject to extensive metabolism; thus bioavailability is only about 20%. Three pharmacologically active metabolites have been identified: hydroxy-nefazodone, triazoledione and m-chlorophenylpiperazine (mCPP), which all possess significant affinities for the 5HT$_{1A}$ receptor. CYP3A4 is primarily responsible for the metabolism of nefazodone, hydroxy-nefazodone and triazoledione while mCPP is primarily metabolised by CYP2D6 (Greene and Barbhaiya 1997). The pharmacokinetics of nefazodone and hydroxy-nefazodone, but not mCPP, are nonlinear. Peak plasma concentrations occur at about one h; the mean $t_{1/2}$ of nefazodone is 2 to 4 h (mean value 3 h) (FDA Approved Drug Products 2011). Although nefazodone exhibits nonlinear pharmacokinetics, steady-state plasma concentrations are attained within 4 days of initiation of drug administration or change in dose. Nefazodone inhibits CYP3A4 and is a weak inhibitor of CYP2D6. Its pharmacokinetics is not

appreciably altered in patients with renal or mild-to-moderate hepatic impairment. However, nefazodone plasma concentrations are increased in severe hepatic impairment and in the elderly, especially in elderly females. Lower doses of nefazodone may be necessary in these groups (Greene and Barbhaiya 1997). It should be mentioned that nefazodone is restricted in many countries and seldom used, also because of its hepatoxicity.

There have been no reports of any relationship between plasma or serum concentrations of nefazodone and antidepressant response (Mitchell 2004). However, nefazodone exhibits an ascending dose-response curve so that while at lower doses (300–400 mg/day) its efficacy is similar to that of the SSRIs, at higher doses (500 mg/day), it has been suggested to provide a greater extent of effectiveness than the SSRIs (Preskorn SH 1995; Horst and Preskorn 1998). Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone with a reported rate in the United States of about 1 case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of treatment (FDA Approved Drug Products 2011). However, nefazodone appears to be of low toxicity during poisonings (Benson et al. 2000). The AGNP does not provide any TDM recommendation nor therapeutic range for nefazodone (Hiemke et al. 2018). At steady state, the mean minimum concentration of nefazodone that was found in 18 healthy male subjects was 290 ng/mL for 200 mg/day (Marino et al. 1997).

The pharmacokinetics of mCPP, but not nefazodone or the other metabolites, appears to depend on CYP2D6 (Greene and Barbhaiya 1997). The differences in mCPP pharmacokinetic parameters in PM subjects did not affect the time required for nefazodone and its metabolites to attain steady state or the number of adverse experiences in either group of subjects (Barbhaiya et al. 1996). Furthermore mCPP represents only 2% of the plasma concentration, thus no dose adjustment with regard to *CYP2D6* genotype is recommended for nefazodone (Barbhaiya et al. 1996; Kirchheiner et al. 2001).

One PET imaging study is reported using the radiotracers [^{18}F]setoperone and [^{11}C]SCH-23,390 to predict clinical response to nefazodone in patients with major depression and anger attacks (Mischoulon et al. 2002). [^{18}F]setoperone binds to 5-HT2A receptors, whilst [11C]SCH-23,390 binds to D_1 receptors, although it also has appreciable binding to 5-HT2A receptors as well. Nefazodone was administered at doses of 300 to 600 mg/day. This study found a decrease in 5-HT$_2$ binding potential in the right medial frontal and left parietal regions after 6 weeks of treatment (Mischoulon et al. 2002). [^{18}F]setoperone binding decreased by 40–52% after treatment with nefazodone, while binding of [^{11}C]SCH-23,390 was unchanged. Thus, at therapeutic doses, nefazodone occupies 5-HT$_{2A}$ receptors to a considerable extent. Moreover, binding by both radiotracers predicted response to treatment at 6 weeks. Plasma concentrations were not reported in this study.

2.4.9. Reboxetine

Reboxetine is a selective NRI developed as a first-line therapy for MDD (Hajos et al. 2006), although its clinical efficacy has been challenged (Eyding et al. 2010; Cipriani et al. 2018). Reboxetine is a racemic mixture and the (S,S)-(+)-enantiomer is more potent at noradrenaline reuptake inhibition, although the (R,R)-(-)-enantiomer is present at higher concentrations in plasma. Binding studies have documented that reboxetine has no significant affinity for adrenergic, serotonergic, histaminergic or muscarinic receptors. The pharmacokinetics of reboxetine are linear up to a dosage of 12 mg/day (Fleishaker 2000). Reboxetine is rapidly and completely absorbed after oral administration. The peak plasma concentration is achieved within 2 to 4 h and the absolute bioavailability is >94%. The distribution of reboxetine appears to be limited to a fraction of total body water due to its high (>97%) binding to plasma proteins, with a mean terminal $t_{1/2}$ ranging between 12 and 16 h (Fleishaker 2000). Reboxetine is extensively metabolised in the liver through three major pathways, including hydroxylation of the ethoxyphenoxy ring, oxidative dealkylation and oxidation of the morpholine ring, and less than 10% is excreted unchanged in the urine (Fleishaker 2000). According to in vitro studies in human liver microsomes, CYP3A4 is the major isoform involved in reboxetine biotransformation. (Wienkers et al. 1999).

To our knowledge, no study has evaluated the possible correlation between plasma concentrations of reboxetine and its clinical effects in patients with MDD. Following determination of reboxetine enantiomers in patients stabilised on racemic reboxetine, utilisation of enantioselective TDM procedures has been suggested in clinical situations with inadequate drug response (Öhman et al. 2003). The AGNP level of recommendation for the use of TDM for reboxetine is 3 with a therapeutic reference range of 60–350 ng/mL (Hiemke et al. 2018).

To our knowledge, no studies have been performed examining the influence of *CYP3A4* and/or *CYP3A5* genetic polymorphisms on the pharmacokinetics of reboxetine, while *CYP2D6* alleles (*3, *4, *5, and *6) had no influence among patients treated with reboxetine (Kuhn et al. 2007). Considering the pharmacodynamic aspect, no association was found between the SERT-linked polymorphic region (5-HTTLPR) and response to reboxetine treatment (Lewis et al. 2011). However, there are some interesting research findings indicating that a functional deletion polymorphism in the α-$_{2B}$ adrenoceptor gene (*ADRA2B*) has been linked to emotional memory and post-traumatic stress disorder. *ADRA2B* deletion carriers demonstrated enhanced emotional memory for negative stimuli compared with deletion noncarriers. Reboxetine-attenuated enhanced memory for negative stimuli in deletion noncarriers but had no significant effect in deletion carriers in healthy and depressed individuals (Gibbs et al. 2013). On the other hand, emotional memory is impaired in healthy COMT val158met homozygotes and selectively improved in this group by reboxetine. If replicated, these pharmacogenomics aspects might have potential translational implications for the use of reboxetine (Gibbs et al. 2014).

There is no published report on the binding of reboxetine to a molecular target in the human or non-human primate brain. While reboxetine and its derivatives have been labelled extensively for use as PET tracers for the NET (Ding et al. 2005), reboxetine's binding in itself to the NET has not been evaluated with PET.

2.4.10. Tranylcypromine

Tranylcypromine was initially developed as an amphetamine analogue in the 1940s. Its antidepressant activity was discovered ten years later, when it was revealed that this compound acts as an irreversible and non-selective inhibitor of the MAO-A and B (Maass and Nimmo 1959). Tranylcypromine is also an inhibitor of the NET at higher dosages (Hampson et al. 1986). Limited human pharmacokinetic data are available. After administration of a single dose of 20 mg in healthy volunteers, a T_{max} of 1–2 h, a C_{max} ranging between 50 and 70 ng/mL and a mean $t_{1/2}$ of 2 h were observed (Spahn-Langguth et al. 1992). Animal data indicates that tranylcypromine undergoes phase-I metabolism to different compounds (e.g. p-hydroxytranylcypromine, N-acetyltranylcypromine, N-acetyl-p-hydroxytranylcypromine), some of which have weak MAO inhibitor activity (Baker et al. 1999). The role of common CYPs in tranylcypromine biotransformation remains unknown. The co-administration of the potent CYP2D6 inhibitor paroxetine did not modify the plasma concentration of tranylcypromine, thus ruling out a major role of CYP2D6 in its metabolism (Dechant and Clissold 1991). Due to the important difference between pharmacokinetic half-life and pharmacodynamic half-life, no relationship between the plasma concentration of tranylcypromine and clinical response would be expected. For this reason, the level of recommendation for the use of TDM for this drug is 4, with a reference range ≤50 ng/mL and TDM should be restricted to special indications (Hiemke et al. 2018).

It has been shown that, in a family with major depression, four patients who did not respond to TCAs or fluoxetine did respond to tranylcypromine. This suggests that there are yet-to-be-defined genetic factor(s) influencing the pharmacodynamics of tranylcypromine and that previously known antidepressant response of relatives may be a good indicator of the response of the index patient (O'Reilly et al. 1994). This is supported by the finding that first-degree relatives of responders to irreversible monoamine oxidase inhibitors will also usually respond to tranylcypromine (Pare et al. 1962).

An [11C]clorgyline PET study evaluated tranylcypromine MAO-A occupancy after three days of a subtherapeutic dose of 10 mg daily and reported a mean value of 58% (Fowler et al. 1996). This demonstrates brain penetration of tranylcypromine but does not provide guidance to optimise MAO-A occupancy, since from a clinical perspective the dose of tranylcypromine was low.

2.4.11. Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) approved for the treatment of MDD with or without anxiety (Fagiolini et al. 2012). It has a dual mechanism of action involving inhibition of the presynaptic SERT and serotonin type 2 postsynaptic receptor antagonism (5-HT$_{2A}$ and 5-HT$_{2C}$). It is also a histamine H$_1$ and α-adrenergic receptor antagonist, with minimal anticholinergic effects (Stahl 2009). Trazodone is available in different formulations including immediate-release with 2 prolonged release drug products (Fagiolini et al. 2012; Goracci et al. 2016).

Peak plasma concentration is reached after one hour with the immediate-release form, and 4 and 8 h with the two prolonged-release forms, respectively (Fagiolini et al. 2012; Goracci et al. 2016). The biotransformation of trazodone is mediated mainly by CYP3A isoforms, yielding m-chlorophenylpiperazine (*m*CPP) as the major active metabolite (Rotzinger, Fang, Baker 1998) *m*-CPP, metabolised by CYP2D6 (Rotzinger, Fang, Coutts, et al. 1998) has a serotonin-releasing

effect and agonistic effects for various 5-HT receptor subtypes (Mihara et al. 2002). The $t_{1/2}$ of trazodone is short (6.6 h), while it is increased with the prolonged-release form (about 12 h) (Fagiolini et al. 2012). In elderly patients, the $t_{1/2}$ of trazodone is increased (Greenblatt et al. 1987).

There are large interindividual variations in the steady-state plasma concentrations of trazodone and m-CPP in patients receiving the same dose of trazodone (Mihara et al. 2002). The relationships between trazodone and m-CPP plasma levels and the clinical effects were studied in 26 patients with major depression during treatment for three weeks with 150 mg/day trazodone immediate-release at bedtime using an open-study design. The proportion of responders was significantly higher in the group with trazodone concentrations above 700 ng/mL (12 h after the last dose intake). No significant association was observed between side effects and trazodone plasma levels, but the concentration range was limited. The m-CPP levels were not correlated with therapeutic response or side effects (Mihara et al. 2002). In elderly patients receiving 150 mg/day trazodone immediate-release in three doses ($n = 11$), a threshold plasma concentration of trazodone before the morning dose of 650 ng/mL was deemed necessary for a good antidepressant response after five weeks (Monteleone et al. 1989). As these studies were performed with the immediate-release formulation, the target concentrations might be different with prolonged formulations. The AGNP level of recommendation to use TDM for trazodone is 2 with a therapeutic reference range of 700–1000 ng/mL (Hiemke et al. 2018)

No studies have been performed examining the influence of CYP3A4 and/or CYP3A5 genetic polymorphisms on the pharmacokinetics of trazodone, while genetic polymorphisms in the 5′-flanking region of the CYP1A2 gene and in the CYP2D6 gene were not associated with plasma trazodone or m-CPP levels (Mihara, Otani, Suzuki, et al. 1997; Mihara et al. 2001).

There is no published report on the binding of trazodone to a molecular target in the human or non-human primate brain although the pharmacokinetics of trazodone and mCPP in rat brains has been described (DeVane et al. 1999).

2.4.12. Vilazodone
Vilazodone is a new antidepressant approved by the FDA for the treatment of MDD. It is a novel dual-acting serotonergic antidepressant that combines selective serotonin reuptake inhibition with partial agonism of the 5-HT$_{1A}$ receptor (Dawson and Watson 2009; Khan 2009). The pharmacokinetics of vilazodone at

doses ranging from 5 mg to 80 mg are dose-dependent after single and multiple administrations (Frampton 2011). Vilazodone concentrations peak at a median of 4–5 h (T$_{max}$) after administration and decline with a terminal $t_{1/2}$ of approximately 25 h. The absolute bioavailability of vilazodone is 72% with food. Administration of vilazodone with food (high fat or light meal) increased C$_{max}$ by approximately 147–160% and AUC by approximately 64–85%. Vilazodone is widely distributed and highly bound to plasma proteins (96–99%). Vilazodone is extensively metabolised through CYP and non-CYP pathways (possibly by carboxylesterases), with only 1% of the dose recovered in the urine and 2% of the dose recovered unchanged in the faeces (Frampton 2011). CYP3A4 is primarily responsible for its metabolism among CYP pathways, with minor contributions from CYP2C19 and CYP2D6 (Frampton 2011). In vitro studies with human microsomes and human hepatocytes indicate that vilazodone is unlikely to inhibit or induce the metabolism of other CYPs except for potential inhibition of CYP2C8. Strong inhibitors of CYP3A4 (e.g. ketoconazole) can reduce the metabolism of vilazodone in vivo and increase exposure (Boinpally et al. 2014); the dose of vilazodone should, therefore, be decreased up to 50%. Conversely, strong inducers of CYP3A4 (e.g. carbamazepine) can decrease vilazodone exposure (Boinpally et al. 2014) and should, therefore, be accompanied by a dose increase up to 80 mg/day (Boinpally et al. 2014). So far, no study has investigated the association between plasma concentrations of vilazodone and clinical outcome in patients with MDD. Vilazodone steady-state concentrations in blood that may be expected under a dose of 40 mg/day will amount to $35 - 67$ ng/mL (Hiemke et al. 2018).

As expected, impaired renal function does not affect the pharmacokinetics of vilazodone, while severe hepatic impairment led to vomiting in 4/8 patients treated with vilazodone, as opposed to 0/8 patients with severe hepatic impairment not treated with vilazodone (Boinpally et al. 2013; Boinpally et al. 2015). It has been reported that polymorphisms or SNP haplotypes affect the therapeutic response and the incidence of nausea and vomiting upon treatment with vilazodone (Rickels et al. 2009; Lindsey 2011). However, the exact SNP(s) and gene(s) have not been specified, and termed only Marker 1 and Marker 2 (Rickels et al. 2009); thus, the report does not meet generally accepted scientific standards for the reporting of results. Considering the major involvement of CYP3A in vilazodone metabolism, it is also not

expected that variations in CYP3A genes could account for the reported findings.

Vilazodone shows potential to enhance serotonin neurotransmission through a blockade of the SERT as well as a direct partial agonism at $5HT_{1A}$-receptors (Schwartz et al. 2011). This model of $5HT_{1A}$ partial agonism seems to be corroborated by animal (rat) studies of vilazodone (Schwartz et al. 2011). Other animal studies showed decreased potential by vilazodone to penetrate the blood-brain barrier following a single-dose administration (Schwartz et al. 2011). Multiple doses seemed to improve the penetration significantly; it can be hypothesised whether some saturation of transporters such as PGP could explain this finding (Bundgaard et al. 2016). In a study, only two of six subjects showed plasma levels higher than 50 ng/mL (Rabiner et al. 2000), when treated with 40 mg single-dose vilazodone. The occupancy of the 5-HT_{1A} receptor in these two patients was 58% and 47% for the 5-HT_{1A} autoreceptor, and 24% and 32% for the 5-HT_{1A} postsynaptic receptor, respectively.

2.4.13. Vortioxetine

Vortioxetine exhibits a multimodal mode of action, with a direct receptor modulation (being a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist; 5-HT_{1B} receptor partial agonist; 5-HT_{1A} receptor agonist) and inhibition of the SERT. The recommended dose range in the treatment of MDD is $5 - 20$ mg/day. Vortioxetine is slowly but well absorbed after oral intake exhibiting dose-proportional pharmacokinetics and reaching maximum plasma concentrations after 7 to 11 h, with an absolute bioavailability around 75%, with no effect of food on its pharmacokinetics. The mean $t_{1/2}$ is 57 h (Connolly and Thase 2016)(Areberg et al. 2012b).

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent by CYP3A4/5 and CYP2C9, leading to pharmacologically inactive metabolites and subsequent glucuronic acid conjugation (Areberg, Sogaard, et al. 2012; Hvenegaard et al. 2012). The maximum recommended dose is 10 mg/day in known CYP2D6 PMs. In CYP2D6 UMs, the plasma concentrations of vortioxetine at 10 mg/day were between those obtained in EMs at 5 mg/day and 10 mg/day (Chen et al. 2018). Although no clinical study reports an association between the *CYP2D6* polymorphism and clinical response to vortioxetine, a lower dose of vortioxetine may be considered if a CYP2D6 inhibitor (e.g. bupropion, quinidine) is added to vortioxetine (Chen et al. 2013). A dose adjustment of vortioxetine may also be considered if a broad cytochrome P450 inducer (e.g. rifampicin, carbamazepine, phenytoin) is added to vortioxetine (Chen et al. 2013). When vortioxetine is co-administered with CYP3A4 inhibitors (ketoconazole) and CYP2C9 inhibitors (fluconazole), no dose adjustment is needed. Based on the available literature, no other polymorphisms than those of *CYP2D6* are consistently relevant to prescription of vortioxetine in clinical practice. Vortioxetine itself did not show inhibitory or induction effects on CYP isoforms and has, therefore, a low potential for clinically relevant pharmacokinetic interactions with other drugs (Brintellix: European Public Assessment Report: Summary of product characteristics 2014). The AGNP level of recommendation for the use of TDM for vortioxetine is 2 with a therapeutic reference range of 10–40 ng/mL (Hiemke et al. 2018)

Two PET studies were performed in healthy volunteers both after single and after multiple doses of vortioxetine for assessment of occupancy of the SERT and the 5-HT_{1A} serotonin receptor, at which vortioxetine acts as an agonist (Areberg, Luntang-Jensen, et al. 2012; Stenkrona et al. 2013). In the first study, SERT occupancy was assessed in a large group ($n = 46$) of healthy volunteers in the midbrain. After single doses, 2.5 mg vortioxetine was associated with 29% occupancy of the SERT, 10 mg with 44%, and 60 mg with 70% (Areberg, Luntang-Jensen, et al. 2012). Occupancy values after multiple dosing (9 or 13 days, respectively) were higher, being 35–49% at 2.5 mg, 51% at 5 mg, 63% at 10 mg, 90% at 20 mg and above 95% at 60 mg. From those data, an EC_{50} value of 4.8 ng/mL was calculated. The oral dose needed to occupy 50% of the SERT was calculated to be 8.5 mg (Stenkrona et al. 2013). The 5-HT_{1A} receptor was not measurably occupied by 30 mg of vortioxetine (Stenkrona et al. 2013). Taken together, the available data suggest that the SERT is occupied to a lower extent by vortioxetine than by the SSRIs at the lower end of the clinically used dose range ($5 - 20$ mg). 80% of the SERT are occupied at plasma concentrations of 20–30 ng/mL, and the high dose almost completely occupies the SERT. The clinical efficacy at the 5 mg dose, at which the SERT is occupied to an extent of just 50% or even less, has been attributed to almost complete saturation of the 5-HT_3 receptor by vortioxetine at this dose (Sanchez et al. 2015). PET studies on target engagement of the 5-HT7 serotonin receptor by vortioxetine are lacking.

3. Specific topics

3.1. Non-antidepressants in bipolar depression and augmentation in major depression

This section briefly focuses on augmentation agents for treatment-resistant major depression or bipolar

depression. The FDA has approved aripiprazole, brexpiprazole, quetiapine, the combination olanzapine/fluoxetine and, recently, esketamine for treatment-resistant MDD. Depression guidelines do not agree on the role of augmentation agents. In 2015, a review of the literature on 11 augmentation agents for treatment-resistant depression was published (Zhou X et al. 2015), describing quetiapine, aripiprazole, thyroid hormone and lithium as more efficacious than placebo. The FDA has approved monotherapy or adjunct for lurasidone and monotherapy for quetiapine for treatment in bipolar depression. Cariprazine was also recently approved for the treatment of depressive episodes associated with bipolar I disorder in adults. Various authors and guidelines recommend different options for bipolar depression. In 2014, a review acknowledged that, for bipolar depression, controlled trials of non-antidepressant treatments remain scarce, but findings with olanzapine/fluoxetine, lurasidone, quetiapine, and perhaps carbamazepine and valproate were encouraging, while lithium required more adequate testing (Selle et al. 2014). The positive trials of augmentation in depression with thyroid hormones are limited to T_3 prescription in patients taking TCAs (Connolly and Thase 2011). Aripiprazole, lithium and lurasidone are not described individually in this guideline but are briefly reviewed.

3.1.1. Ketamine/esketamine:

Ketamine, a dissociative anaesthetic, was developed as a safer alternative to phencyclidine, with less propensity for hallucinations or unpleasant psychotic side effects. It is mostly prescribed as a racemate containing both (S)-ketamine (esketamine) and (R)-ketamine, while intranasal (S)-ketamine is marketed for treatment-resistant depression (Zanos et al. 2018). Ketamine's main pharmacological effect is thought to be a non-competitive antagonism at the NMDA-receptor (phencyclidine binding site), with esketamine having a 3- to 4-fold higher affinity for the NMDA receptor than (R)-ketamine (Singh et al. 2016). Animal data also demonstrated antidepressant-like effects facilitated by sustained activation of glutamatergic AMPA receptors through ketamine's metabolite (2 R, 6 R)-hydroxynorketamine independent of ketamine's NMDA receptor inhibition (Zanos et al. 2016). Because ketamine has been used as an anaesthetic for over 40 years at dosages two to five times higher than those applied in antidepressant treatment regimes, toxicity, possible side effects and pharmacokinetic characteristics are well known. Oral ketamine undergoes extensive first-pass liver metabolism (mainly by

CYP3A4 and CYP2B6) to its active but less potent metabolite norketamine, resulting in a bioavailability of approximately 16%. Ketamine $t_{1/2}$ is around 2–2.5 h (Mathew et al. 2012). Intranasal esketamine is rapidly absorbed by nasal mucosa and reach maximum plasma concentration after 20 to 40 min as described in the summary of product characteristics. For antidepressant use of ketamine only sub-anaesthetic dosages are used, and incidence of serious adverse advents was very low, with no severe psychotic symptoms reported. Dissociative symptoms such as feeling outside of their bodies or reported altered perception of time can occur but are entirely reversible (Kraus et al. 2017).

In vitro, it has been found that genetic variants of *CYP2B6* and, to a lesser extent, *cytochrome P450 oxidoreductase* diminished ketamine N-demethylation activity, without affecting the stereoselectivity of its metabolism (S > R) (Wang PF et al. 2018). To our knowledge, there are presently no clinical studies assessing whether genetic polymorphisms of these two and/or of other genes could influence ketamine pharmacokinetics, therapeutic and/or unwanted effects.

Data on plasma concentrations of ketamine in relation to antidepressant effects are so far lacking. For a dose of 0.5 mg/kg infused over 40 min, maximal plasma concentrations were 177 ± 54 ng/mL in patients with bipolar disorders and 204 ± 101 ng/mL in patients with major depression (Zanos et al. 2018). Blood concentrations of (R,S)-ketamine and its major metabolites (R,S)-norketamine and (R,S)-dehydronorketamine are highly variable between individual patients. Measuring ketamine plasma levels to improve therapeutic response or tolerability, however, is not established and expected to have limited value due to the rapid onset of action. In theory it could be useful for distinct patients (e.g. patients who do not respond or who exhibit unwanted adverse reactions), especially dissociative and psychotomimetic effects.

Because of the lack of a validated radiotracer for the NMDA glutamate receptor, studies on the engagement of this compound with its primary target are completely lacking. However, ketamine's effects on other neurotransmitter systems have been characterised quite extensively. While some studies show a reduction in D_2 receptor availability following ketamine administration, indicating a ketamine-induced dopamine release (Tsukada et al. 2000), other studies were not able to confirm this finding (Kegeles et al. 2002; Vernaleken et al. 2013). One study in monkeys showed a reduction in D2 receptor availability after a

single dose of esketamine but not R-ketamine (Hashimoto et al. 2017). It was also demonstrated that ketamine administration reduces availability of one metabotropic glutamate receptor (mGluR5) by 15–20%, and that in patients with depression this reduction was associated with the compound's anti-depressant effects (Esterlis et al. 2018). However, at present the imaging literature does not provide information for personalisation of treatment with esketamine or R-ketamine, specifically on the relationship between target engagement and clinical effects.

3.1.2. Lamotrigine

Lamotrigine is used as an antiepileptic and a mood stabilising drug for bipolar depression. It mainly acts via a blockade of voltage-sensitive sodium channels and inhibition of glutamate release (Rambeck and Wolf 1993). Lamotrigine is rapidly absorbed from the gastrointestinal tract with peak concentration occurring approximately 3 h post-dose and with almost complete bioavailability (Rambeck and Wolf 1993). It is metabolised predominantly by glucuronidation, its main metabolite being the N-2 glucuronide conjugate formed by UGT1A4 and, to a lesser extent, by UGT2B7 (Rambeck and Wolf 1993; Rowland et al. 2006). The pharmacokinetics of lamotrigine is linear and age-dependent, the elderly showing a 30% reduced clearance compared to adults (Johannessen and Tomson 2006). Its pharmacokinetics are similarly altered by pregnancy, as well as hepatic and renal dysfunction (Johannessen and Tomson 2006). The mean $t_{1/2}$ of lamotrigine is 25 h after multiple doses and is affected by concomitant medications (Lamictal (lamotrigine) - FDA 1994). Glucuronidation-inducing co-medications, such as carbamazepine, enhance lamotrigine clearance, leading to shortening of its $t_{1/2}$ to approximately 15 h. Ethinylestradiol also induces glucuronidation of lamotrigine. On the other hand, valproic acid, a potent inhibitor of lamotrigine glucuronidation, can increase lamotrigine concentrations by 200% and prolong its $t_{1/2}$ up to 60 h (Johannessen and Tomson 2006).

The AGNP level of recommendation for the use of TDM for lamotrigine is 2 with a therapeutic reference range of 3–14 μg/mL (Hiemke et al. 2018), as proposed by Morris et al. for anticonvulsive treatment (Morris et al. 2004). In addition, lamotrigine concentrations above 20 μg/mL have been associated with an increased risk of toxicity, although such concentrations are often well tolerated (Hirsch et al. 2004). Only a few recent reports have considered lamotrigine TDM in psychiatry and suggested that lower lamotrigine concentrations in bipolar disorder than in neurology may

be sufficient for therapeutic benefit (Walden et al. 2000; Katayama et al. 2014; Unholzer and Haen 2015). However, as in epilepsy (Johannessen and Tomson 2006), an overlap of lamotrigine concentrations between responders and non-responders has been reported and further studies are needed to confirm the efficacy of a lower therapeutic window in psychiatry (Walden et al. 2000; Katayama et al. 2014; Unholzer and Haen 2015).

Since lamotrigine is mainly prescribed for epilepsy, all pharmacogenetic investigations have been carried out in epileptic patients. Plasma levels of lamotrigine in patients with the *UGT1A4* 142TT genotype were higher than in patients carrying the 142TG or 142GG genotypes, suggesting lower metabolism of lamotrigine by the *UTGT1A4 TT* genotype (Gulcebi et al. 2011; Chang Y et al. 2014). In addition, the *UGT2B7* −161 CT or TT genotypes have a lower apparent clearance of lamotrigine compared to those carrying the −161 CC genotype (Singkham et al. 2013). Patients carrying the *UGT2B7* -161CC or CT genotype showed lower lamotrigine concentration-to-dose ratios than those with the TT genotype when age and co-medications were taken into account (Blanca Sanchez et al. 2010). Twelve SNPs in genes involved in lamotrigine metabolism and transport pathways, including *UGT2B7, ABCB1, ABCG2, NR1I2* and *HNF4α*, were genotyped in 140 Chinese epilepsy patients. Polymorphisms in *ABCG2* rs2231142, rs3114020, *HNF4α* rs2071197 and *ABCB1* rs1128503 were found to be associated with lamotrigine concentration-to-dose ratio normalised by body weight. *ABCG2* rs2231142 might contribute up to 4.8% of the variability of lamotrigine and to the inter-ethnic difference in lamotrigine pharmacokinetics (Zhou Y et al. 2015). Regarding adverse drug reactions, *HLA-A*3101* does not appear to be a predictor for lamotrigine-induced cutaneous adverse drug reactions in Europeans (McCormack et al. 2012), but HLA-B*15:02 was associated with lamotrigine inter alia Stevens-Johnson syndrome in Asian populations, indicating that pre-treatment testing may prevent this severe side effect (Bloch et al. 2014; Deng et al. 2018).

There is no published report on the binding of lamotrigine to a molecular target in the human or non-human primate brain.

3.1.3. Quetiapine

Quetiapine is used for the treatment of schizophrenia, bipolar disorder including bipolar depression and as augmentation therapy in MDD. It is a 5-HT$_{2A}$, D$_1$ and D$_2$ antagonism while its metabolite, norquetiapine, is a noradrenaline reuptake inhibitor and a 5-HT$_{1A}$ partial

agonist, the latter two mechanisms probably contributing to the antidepressant activity of quetiapine (quetiapine is also the indication for MDD in a few countries). It is readily absorbed after oral administration, with a bioavailability of about 70%. After intake of the IR preparation, T_{max} is reached within 1–1.5 h and the $t_{1/2}$ is about 7 h. After intake of ER quetiapine, T_{max} occurs at about six hours and the apparent $t_{1/2}$ is around seven hours (Figueroa et al. 2009; Patteet et al. 2012). Quetiapine undergoes extensive metabolism in the liver, and at least 11 metabolites have been identified. 7-hydroxyquetiapine and 7-hydroxy-N-desalkyl-quetiapine are pharmacologically active but present in plasma at only 2–12% of the concentration of the parent compound, and thus unlikely to contribute to the effects of the drug (Patteet et al. 2012). A third metabolite, N-desalkylquetiapine (norquetiapine), has a pharmacological profile (inhibition of NET and partial agonist at $5HT_{1A}$ receptor) suggesting antidepressant activity (Jensen et al. 2008; Lopez-Muñoz and Alamo 2013) and is present in plasma at concentrations similar to those of the parent compound (Bakken et al. 2011). Norquetiapine $t_{1/2}$ is about 11 h (Winter et al. 2008). CYP3A4 is the main isoenzyme involved in quetiapine metabolism, with a minor contribution of CYP2D6 (Patteet et al. 2012). The pharmacokinetics of quetiapine is significantly affected by co-administration of inhibitors and inducers of CYP3A4. There are conflicting data on whether concomitant valproic acid increases concentration-to dose ratios of quetiapine, or not (Spina et al. 2016). Lamotrigine may decrease quetiapine exposure (Spina et al. 2016). There is no established relationship between the plasma concentrations of quetiapine or norquetiapine and treatment response. The AGNP level of recommendation for the use of TDM for quetiapine is 2 with a therapeutic reference range of 100–500 ng/mL (Hiemke et al. 2018), which has been defined for mania and schizophrenia (Hiemke et al. 2018) and is therefore not necessarily valid when quetiapine is prescribed for MDD (monotherapy and/or for augmentation therapy) or for bipolar depression. Based on expected trough concentrations at 24 h (Hiemke et al. 2018) following a once-daily prescription of 150–300 mg/day and of 300–600 mg/day of quetiapine ER for unipolar and bipolar depression, respectively, therapeutic reference concentrations between 50–100 ng/mL and 50–200 ng/ml can be proposed, but this has to be confirmed by future clinical studies (see also below).

Several polymorphisms located in the CYP3A4/5 genes have been investigated in order to explain the variability of quetiapine pharmacokinetics. Carriers of the CYP3A5*3/*3 showed significantly higher C_{max} and AUC, and decreased clearance compared to CYP3A5*1/*1 and CYP3A5*1/*3 carriers after a single-dose administration in healthy male Korean volunteers (Kim et al. 2014). However, these variants as well as CYP3A4*1B, CYP3A4 rs4646437 and CYP3A7*1, were not found to be associated with plasma variability at trough steady-state serum concentrations (Nikisch et al. 2011; Bakken et al. 2015). One study reported that the trough concentration dose ratio was significantly higher in the CYP3A4*22 carriers compared to *1/*1, a result that needs to be further replicated (van der Weide and van der Weide 2014). No influence of CYP2D6 genetic variants on quetiapine pharmacokinetics was found (Nikisch et al. 2011; Bakken et al. 2015). Genetic variants located in the ABCB1 gene (1236 C > T, 2677 T > A and 3435 C > T) were also investigated, with discrepancies in results across studies. With regard to the antidepressant activity, as norquetiapine is the relevant compound, studies examining the transport of norquetiapine by PGP would be relevant but are presently lacking. Only the 3435 C > T polymorphism showed significant results in two studies, in which CC carriers had a higher AUC and plasma steady-state concentration (Nikisch et al. 2011; Gonzalez-Vacarezza et al. 2013). The latter association was not replicated in two other studies (Kim et al. 2014; Bakken et al. 2015). Several mutations located on genes such as the SV2C, KCNMA1, COMT, have been investigated on quetiapine's antipsychotic activity (Liu et al. 2012; Ramsey et al. 2013; Xu Q et al. 2016), however, no pharmacogenetic studies of antidepressant activity have been published so far. There are no genotype-based dose recommendations for quetiapine available. It is notable that the highest level of evidence in the PharmGKB database for quetiapine was the rs489693 located in the MC4R gene, and associated with weight gain. The latter was annotated as level 2B evidence indicating that this genetic marker needed to be further replicated before implementation in clinical practice (Variant annotations 2020)

Quetiapine's binding to dopamine D_2 receptors has been extensively characterised with PET, and a detailed review of these binding properties is reviewed elsewhere (Gründer et al. 2011). Briefly, quetiapine shows a D_2 receptor binding profile most similar to clozapine. Its binding to striatal D_2 receptors even at very high doses is only modest, and washout from the brain is rapid. In one study, plasma concentrations of quetiapine as high as 800 ng/mL were associated with striatal D_2 receptor occupancies not exceeding 60%, while extrapyramidal side effects (EPS)

were not observed. However, extrastriatal (i.e. cortical and thalamic) D_2 receptor binding was significantly higher than striatal (Vernaleken et al. 2010).

While a therapeutic reference range of $100 - 500$ ng/mL, as suggested by the AGNP (Hiemke et al. 2018), is in good agreement with the available PET studies in schizophrenia, a therapeutic reference range for the treatment of bipolar depression or MDD has not yet been established. It has been hypothesised that the binding of norquetiapine to the NET is the basis for quetiapine's efficacy in affective disorders (Nyberg et al. 2013). The parent compound does not bind to the NET. Quetiapine XR was administered to nine healthy volunteers at doses of $150 - 300$ mg for a duration of 6–8 days, and NET occupancy was measured with the NET-specific radioligand (S,S)-[^{18}F]FMeNER-D2. The mean NET occupancy at 150 and 300 mg was 19 and 35%, respectively (Nyberg et al. 2013). The estimated plasma concentration of norquetiapine corresponding to 50% NET occupancy was 161 ng/mL. While it is presently unclear, whether such very modest NET occupancy leads to antidepressant activity, a therapeutic reference range for norquetiapine remains to be established. Finally, in a PET study with [^{11}C]doxepine, very low single oral doses of 2.5 and 25 mg quetiapine occupied 56–81% of cortical H_1 histamine receptors in healthy humans (Sato et al. 2015).

3.1.4. Aripiprazole, lithium, lurasidone

Aripiprazole: Aripiprazole is a partial D_2 agonist first approved for schizophrenia. Its 5-HT$_{1A}$ partial agonism may contribute to its antidepressant properties (Spina and de Leon 2014). In the majority of patients, aripiprazole is mainly metabolised by CYP2D6 and CYP3A4 to the main active metabolite dehydroaripiprazole. Mean elimination half-live is 75 h for aripiprazole and 94 h for dehydroaripiprazole (Abilify (aripiprazole) - FDA 2002). In CYP2D6 PMs, CYP3A4 is the only metabolic pathway available. Adding a potent CYP3A inducer, such as carbamazepine, requires doubling the aripiprazole dose to maintain the same plasma concentrations and CYP3A4 becomes the major metabolic pathway (de Leon et al. 2012). A PubMed search for aripiprazole augmentation in depression provided no articles on genotyping, TDM or brain imaging. Assuming that an aripiprazole dose of 3–15 mg/day is effective for augmentation (Horikoshi et al. 2019) drug concentrations expected in blood should amount by mean to 40 to 200 ng/mL for aripiprazole and to 16 to 80 ng/mL for dehydroaripiprazole. The combination of aripiprazole with some antidepressants may increase plasma concentrations of aripiprazole and its main metabolite, dehydroaripiprazole. Fluoxetine and paroxetine are typically associated with decreased aripiprazole metabolism by 50 percent, requiring cutting the aripiprazole dose in half as suggested by the summary of product characteristics. Duloxetine and TCAs, as moderate CYP2D6 inhibitors, could be clinically relevant inhibitors of aripiprazole metabolism. Fluvoxamine and high doses of sertraline can be clinically relevant inhibitors of aripiprazole metabolism in some patients (Spina and de Leon 2014).

Lithium: Lithium was the first mood stabiliser and is thought to act at the second-messenger level, particularly at the inositol-signaling mechanisms. In some way, lithium increases serotonergic activity since its combination with antidepressants increases the risk of serotonin syndrome. Therefore, a pharmacodynamic interaction with serotonergic activity may contribute to its possible antidepressant activity in bipolar depression and as an augmentative agent in depression. Limited data also suggest that lithium may potentiate the effectiveness and adverse drug reactions of antipsychotics and antiepileptics with mood-stabilising properties. Lithium is almost exclusively eliminated unchanged in urine and has a mean $t_{1/2}$ of 12 h (Lithium carbonate tablets USP, Lithium carbonate capsules USP, Lithium oral solution USP - FDA 2011). No major pharmacokinetic drug interactions are expected with antidepressants, antipsychotics or antiepileptics with mood-stabilising properties (Oruch et al. 2014). Similar therapeutic reference concentrations as for maintenance treatment in bipolar disorders (between $0.5 - 0.8$ mmol/L) can be proposed for antidepressant potentialisation (Hiemke et al. 2018). A PubMed search for lithium treatment as an augmentation agent in bipolar depression or depression provided no data on pharmacogenetics, but a pilot brain imaging study suggested that lithium may increase hippocampal glutamate in bipolar depression (Zanetti et al. 2015), the same serum lithium concentrations are suggested for augmentation in depression as in bipolar maintenance (Zullino and Baumann 2001; Nelson et al. 2014).

Lurasidone: Lurasidone is a D_2 antagonist first approved for schizophrenia. Its 5-HT$_{2A}$ antagonism, high 5-HT$_{2A}$/D_2 ratio and/or 5-HT$_{1A}$ partial agonism may contribute to its antidepressant activity in bipolar depression (Spina and de Leon 2014). Lurasidone is metabolised by CYP3A4 and the $t_{1/2}$ is about 18 h (Latuda (lurasidone hydrochloride) - FDA 2010). After adding a potent CYP3A inducer, such as carbamazepine, it would require very high dose increases (≥ 5

times) to maintain the same plasma concentrations (de Leon et al. 2012). A PubMed search for lurasidone in monotherapy or as an adjunct for augmentation in bipolar depression provided no data on genotyping, TDM or brain imaging. Therapeutic reference range of $5 - 30\,ng/mL$ is suggested by the AGNP (Hiemke et al. 2018) for an antipsychotic activity. Based on the labelled doses for bipolar depression (20–120 mg/d in USA and 20–60 mg/d in Switzerland), a therapeutic reference range of 2–20 ng/ml can be suggested but this has to be confirmed by future clinical studies.

3.2. Enantiomers

Several antidepressants present as chiral compounds are available as racemates (and, in parentheses, also as single enantiomers): bupropion, citalopram (escitalopram), fluoxetine, mianserin, milnacipran (levomilnacipran), mirtazapine, reboxetine, trimipramine and venlafaxine. Two conditions suggest a clinical benefit for TDM of individual enantiomers of chiral antidepressants: 1. Qualitative and/or quantitative differences in the enantiomers' a) pharmacology (mechanism of action, therapeutic effects, risk for adverse effects), b) metabolism and pharmacokinetics, clinically useful pharmacokinetic data such as dose-dependent drug plasma concentrations or 'therapeutic ranges'; 2. The assay as a tool for phenotyping patients.

These conditions are illustrated with escitalopram which is also available as an antidepressant. This eutomer escitalopram is considerably more potent as a serotonin reuptake inhibitor than the distomer R-citalopram (Bjerkenstedt et al. 1985; Hyttel et al. 1992). The latter unfavourably influences the binding of escitalopram to the SERT by an allosteric mechanism (Mork et al. 2003; Sanchez 2006); this mechanism possibly impairs the clinical efficacy of citalopram. With similar escitalopram serum concentrations (reached after repeated 20 mg/day citalopram or 10 mg/day escitalopram), brain imaging studies show that the occupancy of the SERT in human is higher with escitalopram than with citalopram (Klein et al. 2007; Kasper et al. 2009), despite apparently no stereoselectivity in PGP-controlled transport of citalopram from blood to brain (Karlsson et al. 2013). After administration of citalopram, R-citalopram displays a longer $t_{1/2}$ than escitalopram (47 vs 35 h) (Sidhu et al. 1997). In patients treated with citalopram, R-citalopram generally reaches almost twice the plasma and CSF concentrations as those of escitalopram (Bondolfi et al. 2000; Nikisch et al. 2004). In a study examining the drug level-response relationship in citalopram-treated

patients (Dufour et al. 1987), the used non-stereoselective analysis of citalopram means that the observed drug concentrations reflect those of a mixture of compounds (R-citalopram, escitalopram) which differ in their serotonin-reuptake inhibitor properties. Therefore, it may be concluded that under routine TDM conditions, the drug concentration that is measured and communicated together with the therapeutic reference range (Hiemke et al. 2018) mainly comprise the non-effective R-citalopram.

On the other hand, in a study examining the plasma concentration-response relationship, plasma concentrations of S-, R- or S,R-citalopram did not aid in separating responders from non-responders (Nikisch et al. 2004). In 22 depressed patients treated with 40 mg/day citalopram for 28 days, plasma concentrations of escitalopram and R-citalopram were reported to be $21.6 \pm 10.7\,ng/mL$ and $44.5 \pm 13.6\,ng/mL$ (mean ± SD), respectively, but no 'therapeutic reference range' could be defined. In the context of methadone treatment, one of the main arguments for recommending stereoselective monitoring of its plasma concentrations resides in the fact that the pharmacologically (as an opioid) 'inactive' S-methadone appears to be mainly responsible for QTc-prolongations (Eap, Bourquin, et al. 2000; Eap et al. 2007). However, while citalopram induces more seizures after overdose than escitalopram (Yilmaz et al. 2010), both citalopram and escitalopram, can well increase the QTc interval (Hasnain et al. 2013). Present evidence does not suggest relevant differences between the effects of the enantiomers of citalopram on the QTc interval (FDA drug safety comunication: Revised recomendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses 2012). This means that, while R-citalopram does not contribute to the clinical efficacy of citalopram, it seems to participate dose-dependently to its cardiotoxicity (Keller 2013). However a plasma concentration-adverse effect relationship for R-citalopram has not yet been established. In conclusion, the stereoselective analysis of citalopram for routine monitoring purposes cannot be recommended, but further research is needed on the contribution of R-citalopram on the toxicity of the racemate. Finally, citalopram is stereoselectively metabolised by MAO-A and MAO-B in the human liver, thrombocytes and in the brain (Kosel et al. 2002).

Citalopram can be considered a candidate probe for CYP2C19 phenotyping, since CYP2C19 rather metabolises S-citalopram than R-citalopram. After administration of citalopram, the S-citalopram/R-

citalopram ratio measured in plasma allows the discrimination of CYP2C19 EMs from PMs (Herrlin et al. 2003). In this study, there was a highly significant correlation between this ratio and the S/R-ratio of urinary mephenytoin in mephenytoin-phenotyped patients (note: this antiepileptic drug is no longer marketed, and omeprazole being used as the main CYP2C19 probe drug).

For most of the other chiral antidepressants, present knowledge of differences between enantiomers in mechanism of action, metabolism and pharmacokinetic properties is scarce and studies on stereoselective drug monitoring are lacking, but are briefly summarised below.

Racemic bupropion and hydroxybupropion inhibit noradrenaline and dopamine uptake with similar potency, but the most potent compound is (+)-(2S, 3S)-hydroxybupropion (radafaxine) rather than the parent substance or (-)-(2S, 3R)-hydroxybupropion (Damaj et al. 2004; Hansard et al. 2011). The biotransformation of bupropion to this hydroxylated metabolite occurs stereoselectively by CYP2B6 (Xu H et al. 2007; Coles and Kharasch 2008). Bupropion is considered to be a phenotyping probe for CYP2B6 (Kharasch et al. 2008), but data on steady-state plasma concentrations of the enantiomers of bupropion and its metabolites are not available.

Considering the enantiomers of fluoxetine and its metabolite norfluoxetine, S- and R-fluoxetine and S-norfluoxetine (seproxetine) are potent 5-HT uptake inhibitors, in contrast to R-norfluoxetine (Wong DT et al. 1990; Robertson et al. 1991; Wong DT et al. 1993). Panel studies with CYP2D6-phenotyped subjects suggest that CYP2D6 controls the biotransformation of R- and S-fluoxetine and S-norfluoxetine, but not of R-norfluoxetine (Fjordside et al. 1997). On the other hand, during a 3-week treatment course with fluoxetine (20 mg/day) in patients, plasma concentrations of S-fluoxetine and S-norfluoxetine but not those of R-fluoxetine and R-norfluoxetine, significantly differed between PMs and EMs(Eap et al. 2001). A similar study was published by authors who consider R-fluoxetine, S-fluoxetine, and S-norfluoxetine to constitute the 'active moiety' (Scordo et al. 2005).

With regard to mianserin, due to its stronger antagonistic effects at α_1- and α_2-adrenergic receptors and its noradrenaline uptake inhibition properties, S-(+)-mianserin rather than R-(-)-mianserin may be considered as the eutomer but the possible clinical role of the latter should not be neglected (Pinder and van Delft 1983). Several CYP isoforms contribute stereoselectively to the metabolism, including CYP2D6, which

preferentially metabolises S-(+)- rather than R-(-)-mianserin (Dahl et al. 1994; Mihara, Otani, Tybring, et al. 1997; Eap et al. 1998). In responders, S-(+)- but not R-(-)-mianserin plasma concentrations were found to be higher than in non-responders (Mihara, Otani, Tybring, et al. 1997).

The dual reuptake inhibitor milnacipran is a racemic mixture of cis-isomers: 1S, 2R (F2695 (levomilnacipran) and 1R, 2S (F2696) enantiomers. Levomilnacipran is a more potent inhibitor of NA- and 5-HT uptake in rat synaptosomes than racemic milnacipran (Auclair et al. 2013). There are no studies on trough plasma concentrations of the enantiomers of milnacipran in steady-state conditions (only data on C_{max} are available) (Auspar-milnacipran-hydrochloride-120124.pdf 2012).

Due to the complex pharmacology of mirtazapine, it is not clear, whether S-(+)- mirtazapine is the eutomer, and whether R-(-)-mirtazapine contributes to adverse effects such as cardiac toxicity (Brockmoller et al. 2007). Indeed, the α_2-autoreceptor antagonism of mirtazapine resulting in an increase of the firing rate of serotonergic raphe cells and of serotonin release is mainly due to S-(+)-mirtazapine rather than to R-(-)-mirtazapine. However, the drug effect on 5-HT_{1A}-receptor function, the inhibition of α_2-adrenergic heteroreceptors and 5-HT_3-receptors is more pronounced with R-(-)-mirtazapine (Davis and Wilde 1996; McGrath et al. 1998). The metabolism of mirtazapine occurs stereoselectively (Paus et al. 2003; Brockmoller et al. 2007). In healthy volunteers, S-(+)-mirtazapine ($t_{1/2}$ 15.54 ± 4.4 h) was found to be more rapidly eliminated than R-(-)-mirtazapine (23.22 ± 4.9 h) (Wen et al. 2014). In CYP2D6 PMs $t_{1/2}$ of S-(+)-mirtazapine, but not of R-(-)-mirtazapine, is longer than in EMs (18.8 ± 4.7 h vs 9.9 ± 3.1 h) (Timmer et al. 2000). Steady-state trough plasma concentrations of the enantiomers of mirtazapine in CYP2D6-genotyped patients were obtained in several studies (Lind et al. 2009; Jaquenoud Sirot et al. 2012). As the only study which included ratings of depression in the patients did not find a significant drug plasma concentration-response relationship (Jaquenoud Sirot et al. 2012), the assay of mirtazapine enantiomers in clinical routine conditions cannot be recommended but may be useful for specific purposes.

Recent analyses raised serious doubts about the clinical effectiveness of reboxetine as an antidepressant (Eyding et al. 2010; Huhn et al. 2019), and this evidence limits the usefulness of studies on 'therapeutic plasma concentrations'. Reboxetine is a racemic mixture of S,S-(+)- reboxetine and R,R-(-)-reboxetine: S,S-(+)- reboxetine is more potent in

inhibiting noradrenaline reuptake but steady-state plasma concentrations of R,R-(-)-reboxetine are generally twice as high as those of S,S-(+)- reboxetine (Fleishaker et al. 1999; Öhman et al. 2003). Trimipramine, an atypical TCA, has a high affinity for 5-HT$_2$- and dopamine receptors, and given its activity on these systems, L-trimipramine rather than D-trimipramine is probably the eutomer (Gross et al. 1991). Its metabolism occurs stereoselectively by CYP2D6 and CYP2C19 (Eap, Bender, et al. 2000).

The metabolism of venlafaxine to O-desmethylvenlafaxine is of clinical relevance, as the metabolite was also introduced as an antidepressant (desvenlafaxine). However, monoamine reuptake inhibition properties of desvenlafaxine have not been studied. The R-(+)-enantiomer of venlafaxine is somewhat more potent than S-(-)-venlafaxine in inhibiting serotonin reuptake, but it displays little stereoselectivity with regard to noradrenaline reuptake inhibition (Holliday and Benfield 1995). In mice, there is no stereoselectivity in PGP-mediated transport of venlafaxine to the brain (Karlsson et al. 2010). Several investigations show that R-(+)-venlafaxine rather than S-(-)-venlafaxine is preferentially a substrate of CYP2D6 (Eap, Bertel-Laubscher, et al. 2000; Eap et al. 2003; Ciusani et al. 2004; Kingback et al. 2012), while CYP2C19 preferentially metabolises S-(-)-venlafaxine (Karlsson et al. 2015). In CYP2D6 EMs, R-(+)-venlafaxine and S-(-)-venlafaxine concentrations do not clearly differ, but in PMs, those of the eutomer R-(+)-venlafaxine exceed those of S-(-)-venlafaxine (Ciusani et al. 2004). However, stereoselective TDM of venlafaxine is of little clinical relevance for routine purposes but could help to predict the *CYP2D6* genotype of the patient (Gex-Fabry et al. 2004) and to document the effect of strong CYP2D6 inhibitors on the pharmacokinetics of venlafaxine.

In conclusion, while knowledge concerning the stereoselectivity of the pharmacology and metabolism of chiral psychotropic drugs helps to better understand their clinical consequences, the analysis of the enantiomers of most chiral antidepressants is not recommended for routine TDM, especially since these assays are rarely available.

4. Perspectives

4.1. Perspectives of TDM

TDM as a tool for optimising antidepressant pharmacotherapy is available for almost all antidepressant drugs and also for drugs used for augmentation. Highly precise and accurate drug measurement and, if relevant, metabolite concentrations, are possible, within an acceptable time frame (two days) and at an acceptable cost (less than 100 €per test) - in theory. Availability and quality of TDM substantially differ between countries and regions. Knowledge of TDM among clinicians is often insufficient or lacking. This often leads to pre- or post-analytical errors such as blood sampling before reaching steady state, inappropriate requests or misinterpretation of results. In the laboratories TDM is often not well-implemented in the electronic health records or laboratory information system, time intervals between blood collection and reporting of results may be too long, communication between clinicians and laboratories suboptimal or lacking, and pharmacological (especially pharmacokinetic) expertise is not available in the laboratory.

Therefore, transferring knowledge of TDM to users (i.e. training doctors and laboratory staff) is essential (Baumann et al. 2017). Actual knowledge is presented in the TDM guidelines of the AGNP (Hiemke et al. 2018) and in this review. However, it is still not sufficient for successfully applying TDM in practice. We thus recommend training courses using real TDM cases during medical and laboratory studies in order to improve the use and clinical benefit of TDM. Electronic decision support easily available to practitioners should be implemented. Another area that needs improvement is the evidence base for using TDM for antidepressant pharmacotherapy. Clinical studies on the medical and economic benefits of TDM, especially for the newer antidepressant drugs that are now the first-line medications for treating affective disorders, are necessary. With appropriate design, convincing and objective evidence will be obtained to demonstrate that TDM is a valid tool for optimising antidepressant pharmacotherapy.

4.2. Perspectives on pharmacogenetics

For the treatment of depression, genotyping of pharmacokinetic genes (mostly CYP, as no convincing evidence and/or only preliminary data are presently available for other genes) can be useful in selecting the drug and/or modifying dosing for personalised therapy. This is especially important for TCAs, which have relatively well-defined and narrow therapeutic window. TCAs are however nowadays rarely prescribed at full dose as antidepressants in most countries but rather at low doses for pain treatment. Even though the impact of pharmacogenetic tests is less important for other antidepressants, such a strategy appears sound and legitimate for reducing the interindividual

variability in drug exposure and the risks of side effects or insufficient therapeutic response associated with extreme phenotypes (UMs and PMs). CYP genotyping appears more useful when starting treatment. After long-term treatment, the drug best adapted to a patient has possibly already been chosen based on trial-and-error, while drug dosage has been adapted based on effects (Hicks et al. 2013). On the other hand, it is necessary to acknowledge that the activity of some CYP isoforms (e.g. CYP1A2 and CYP3A4) can poorly be predicted by genetic analysis and must instead be determined by phenotyping and/or TDM. Even for drugs mainly metabolised by the polymorphic enzymes CYP2D6 and CYP2C19, the predictive value of a genotype for the pharmacokinetic characteristics in an individual patient remains low in the majority of subjects not belonging to the extreme geno/phenotypes.

Despite a slow beginning, the routine use of CYP genotyping has markedly increased during the past few years in particular because of the present availability of such tests and lowered costs.

A high number of patients must generally be genotyped for CYP isoforms to prevent one single case of a severe side effect or non-response (Crettol et al. 2014). However, there is increasing evidence for the potential utility of CYP genotyping and/or phenotyping, also illustrated by a recent study on *CYP2C19* genotyping and response to escitalopram (Jukic et al. 2018). Most importantly, the decreasing cost of genetic analysis shifts the cost-benefit ratio towards increasing use of multi-CYP tests, also considering that many results can be used life-long. In the future, new pharmacogenetic variants, using GWAS, WES (whole exome sequencing) and WGS (whole genome sequencing) analysis in particular, are likely to be discovered. PRS (polygenic risk score) for risk of depression onset or other PRS related to side effects (e.g. PRS for obesity to estimate risk for weight gain) could become clinically relevant but this remains to be demonstrated. In addition, the influence of other sources of variability including genetic (e.g. copy number variants and micro-RNA), as well as epigenetic factors (e.g. histone deacetylation and gene methylation) will need to be taken into account (Gendep Investigators et al. 2013; Menke and Binder 2014). Pharmacogenetic data related to both pharmacokinetics and pharmacodynamics need to be incorporated as part of comprehensive pharmacological knowledge base of drugs, despite the fact that there are presently insufficient data to support the widespread testing of pharmacodynamic genes. While pharmacogenetic tests may be used on their own to optimise antidepressant treatment, other factors affecting treatment response such as comprehensive clinical evaluations, TDM, phenotyping tests, drug-drug interactions and data obtained from brain imaging studies will remain important for best possible treatment considerations.

4.3. Perspectives of brain imaging

TDM of psychotropic drugs is a very valuable instrument in everyday patient management. Its value is strongly dependent on the validity of the recommended therapeutic reference ranges. For antipsychotics it has been demonstrated that imaging with PET is one of the most powerful tools in determining and validating these reference ranges. Antidepressants are much less well-characterised with regard to their binding to the target molecules they presumably act upon, with the exception of the SSRIs. SSRIs and SNRIs have been shown to occupy 80% or more of the SERT at clinically-used doses. Unfortunately, the relative contribution of NET occupancy to the clinical effects of this class of drugs remains unclear, and it remains unknown whether a threshold occupancy of this target for selective NRI exists. The situation is similar for the DAT and bupropion. The available PET studies raise serious doubts whether the mechanistic view that this compound acts through blockade of the DAT is true. Moreover, the example of clomipramine shows that for some compounds the relationship between target engagement, plasma concentrations and clinical effects remain to be elucidated. This important example even illustrates – because it does not fit at all into our current framework of knowledge on antidepressant drug action – that we might have to rethink our concepts about the mechanism of action of antidepressant drugs, target engagement and plasma concentrations. Multimodal molecular imaging, preferentially used in conjunction with other imaging modalities and assessment of other biomarkers, has the potential to enhance our knowledge of antidepressant drug action, and it is strongly desirable to promote its application in early drug development, but also in further understanding the mechanisms of action in current antidepressants.

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