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REVIEW ARTICLE

New-generation, non-SSRI antidepressants: Drug-drug interactions and therapeutic drug monitoring. Part 2: NaSSAs, NRIs, SNDRIs, MASSAs, NDRIs, and others

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Abstract

After the development of "classical" tricyclic antidepressants and monoamine oxidase inhibitors, numerous other classes of antidepressant drugs have been introduced onto the market. The selective serotonin reuptake inhibitor class is the best-known one, but many others exist, usually identified by their mechanism of activity. In this second part of the review, focused on new-generation antidepressants not included among selective serotonin reuptake inhibitors, the following classes are considered: noradrenergic and selective serotonergic antidepressants; norepinephrine reuptake inhibitors; serotonin, norepinephrine and dopamine reuptake inhibitors; melatonergic agonists and selective serotonergic antagonists; norepinephrine and dopamine reuptake inhibitors; and so forth. These different mechanisms underlie tolerability and safety profiles that can be very different among the classes, with each one providing significant advantages and disadvantages in comparison with others. The main characteristics of the following antidepressants are described: mianserin, mirtazapine, setiptiline, reboxetine, viloxazine, teniloxazine, atomoxetine, nefazodone, agomelatine, bupropion, esketamine, and tianeptine. The paper is focused on their metabolism and interactions, but

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also includes brief notes on analytical methods useful for their therapeutic drug monitoring.

KEYWORDS

drug-drug interactions, metabolism, metabolites, new-generation antidepressants (NGAs), therapeutic drug monitoring (TDM)

1 | INTRODUCTION

Major depressive disorder (MDD) is currently considered one of the most important causes of disability worldwide, especially in late life,[1] and its increasing recognition as a severe, life-threatening disorder is reflected in the rise of expenditures for its pharmacological treatment.[2] This trend is present also in developing countries, underscoring the acknowledgment of MDD treatment as one of the fundamental healthcare services that should be provided to the population.[3]

Effective pharmacological therapies for MDD began in the 1950s with the development of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOI); these classes are now considered to include the "classical," first-generation antidepressants.[4] There is no complete accord on which drugs belong to the second, third or even fourth generation of antidepressants; however, most scientists agree that different MDD treatment paradigms have arisen with the introduction of selective serotonin reuptake inhibitors (SSRIs), in the 1980s. SSRIs and all other agents developed thereafter are usually collectively known as "new-generation" (or sometimes "atypical," by analogy with antipsychotic drug classes) antidepressants (NGAs). [5]

Like MAOIs and then SSRIs, other NGA agents are also usually grouped together according to their mechanism of activity and indicated by the corresponding acronyms, as follows: serotonin and norepinephrine reuptake inhibitors (SNRI); serotonin modulators and stimulators (SMS); serotonin antagonists and reuptake inhibitors (SARI); noradrenergic and selective serotonergic antidepressants (NaSSAs); norepinephrine reuptake inhibitors (NRIs); serotonin, norepinephrine and dopamine reuptake inhibitors (SNDRIs); melatonergic agonists and selective serotonergic antagonists (MASSAs); and norepinephrine and dopamine reuptake inhibitors (NDRIs). Other drugs still are not included in any of these classes, either because their mechanism is still debated, or because no clear path to establish a new class has emerged.

Despite their different mechanisms of action and pharmacological profiles, until the introduction of esketamine and brexanolone (the latter only indicated for postpartum depression) all antidepressant classes were commonly believed to have delayed onset of effect: antidepressant treatment had a latency of at least 3 to 4 weeks before full symptom relief would appear; most patients experienced benefits after about 6 to 12 weeks.[6] This would suggest that the immediate pharmacological mechanism is just the starting point for a much more complex, and as yet unclear, set of adaptive body responses that finally produce the desired effect. These adaptive responses are currently believed to be linked to the activation of second messenger pathways and transcriptional regulators and/or the onset of complex interactions between different neurotransmitter systems.[7,8] It should be noted, however, that the common knowledge of the antidepressant delayed onset of action has been disputed for a long time in the academic community, at least until the 2000s.[9]

In any case, esketamine and brexanolone (which are delivered intranasally or intravenously) seem to have the advantage of an almost immediate clinical response, which appears in a matter of hours or days instead of weeks.[10] No other antidepressant drug has emerged with similarly fast onset of action, even though many candidates are currently being developed.[11]

The huge number of possible choices when beginning a pharmacological antidepressant treatment underscores the need for deepening the knowledge of mechanisms, pharmacodynamic and pharmacokinetic characteristics,

and possible interactions of these drugs. Therapy personalization and optimization is a real necessity for the treatment of such a complex and multifaceted disorder as MDD, one that can really lead to the minimization of the side effect burden and to increased treatment efficacy.[12]

Often, patient compliance is low due to the chronic nature of the MDD therapy, to the side effect burden, to the delayed onset of therapeutic effects and to the hopelessness which is a hallmark of MDD[13]; nonresponder patients often need different drug doses or the switch to another drug. All these and other problems can be tackled effectively through therapy personalization.[14] An optimal personalization will be achieved by using a combination of clinical and genetic factors, a method that has been demonstrated to be cost effective.[15]

One of the most powerful tools for therapy optimization is therapeutic drug monitoring (TDM).[16-18] It includes the periodic determination of drug and metabolite plasma levels, together with the use of chemical-clinical correlations (i.e., correlations between administered drug dose and plasma levels; between plasma levels and therapeutic efficacy; and between plasma levels and side and toxic effects).

The information thus obtained represents a sound, rational and objective foundation, on which the clinician can base its activity using clinical observations to build a safe and effective therapeutic platform.[19] TDM can also lead to reduced healthcare expenses, due to the possibility of better efficacy, increased patient compliance and enhanced safety, leading to a reduction in hospitalizations due to unwanted effects or therapy ineffectiveness.[20] TDM is particularly useful in avoiding overdoses and their consequences, as well as in managing drug-drug interactions (DDIs)[21]: Of course, this is particularly important during polypharmacy.

Currently, regarding psychotropic drugs, TDM has been mainly applied to antipsychotics[22-25] with notable success. Only in the last few years, TDM is becoming widespread in other fields of pharmacopsychiatry and neuropharmacology, including anxiolytic,[26,27] anticonvulsant,[28] and antidepressant[29] pharmacotherapy. Among antidepressants, TDM is becoming relatively common especially for TCAs, MAOIs, and SSRIs, which are the best-known antidepressant drugs, especially in cases of metabolic anomalies, suspected noncompliance, or polypharmacy.[30] TCAs and MAOIs, in particular, have relatively narrow therapeutic windows, thus avoiding toxicity is one of the main purposes of TDM for these drugs.[31] Non-SSRI NGAs are less well-known, and their chemical-clinical correlations are often not well established; for this reason, it is important that suitable analytical methods are developed, to try and make their TDM feasible and reliable and to harvest the large amount of data needed to produce statistically significant chemical-clinical correlations.[29] In particular, some NGAs are not approved in the USA, and this drastically reduces their international scientific appeal, leading to a dearth of papers detailing their use, interactions, and TDM. Starting in 2004, the German Workgroup for Neuropsychopharmacology and Pharmacopsychiatry (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie [AGNP]), has published its TDM Expert Group consensus guidelines,[32] which have been updated in 2011, 2017,[33] and 2019 (the last one only in German for now). There, the authors report for each considered drug a "level of recommendation to use TDM," which is expressed as a number in the 1 to 4 range: 1 corresponds to the drugs for which TDM is most recommended ("Strongly recommended"), followed by 2 ("Recommended"), 3 ("Useful"), and 4 ("Potentially useful"). It should be underscored, and understood, that these recommendation level classes are only relative to routine TDM use. However, the practice can be very useful for a wide range of purposes, not limited to routine applications. For example, TDM usefulness includes, but is not limited to, insufficient response, suggested nonadherence, adverse drug reaction at therapeutic doses, and potential DDIs. This is true even for those drugs whose TDM recommendation level is low, 3 or 4, and even when chemical-clinical correlations are unavailable or unclear. Hence the great clinical and research value of TDM.

In this Part 2 of the review series, the main pharmacodynamic, metabolic, and interaction characteristics will be described for NaSSA, NRI, SNDRI, MASSA, and NDRIs drugs, and namely: mianserin, mirtazapine, and setiptiline among NaSSAs; reboxetine, viloxazine, teniloxazine, and atomoxetine among NRIs; nefazodone as an SNDRI; agomelatine as a MASSA; bupropion as an NDRI; and esketamine and tianeptine outside all other classes. Some notes are also included, dealing with available analytical methods that can be used for TDM purposes.

In Part 1 of the review series,[34] similar information has been reported on SNRI, SMS, and SARI antidepressants.

2 | METHODS

Electronic searches of the following publication databases were conducted: Scopus[35] and PubMed.[36] Search results covered the time span from 2000 to August 2019, to retrieve the most recent and updated information available. If this information proved to be incomplete on in any way unsatisfactory, the search was extended back in time in 5-year intervals.

Search terms for the general section of each drug monograph used the following strings: *drug name* AND (pharmacology OR metabolism OR pharmacokinetics); *drug name* AND (mechanism of action). The results for each drug were then examined in detail, filtering data according to presence in meta-analysis papers and in double-blind, high-numerosity studies (in this order). All other papers were discarded.

Search terms for the analytical/TDM section of each drug monograph used the same time span and the following string: *drug name* AND (HPLC OR LC OR MS OR mass spectrometry OR GC or CE OR electrophoresis OR immunoassay); *drug name* AND (TDM OR monitoring). Within these results, exclusively papers on applications to human blood/plasma/serum or other human biological tissues relevant for TDM purposes were chosen. Only papers with a clear analytical purpose were chosen; that is, those that included complete or almost complete analytical method details and performance data.

3 | NORADRENERGIC AND SELECTIVE SEROTONERGIC ANTIDEPRESSANTS

3.1 | Mianserin

Mianserin ((±)-2-methyl-1,2,3,4,10,14b-esahydrodibenzo[c,f]pyrazino[1,2-a]azepine, MSR, Figure 1A) is an antidepressant and hypnotic marketed in several countries as Tolvon, Lantanon, and Lerivon; generic formulations are also commonly available.

It was first approved in France in 1979 with the name Athymil, and then in the UK as Norval. It was also approved in 1998 in Australia,[37] but has never been approved by the US Food and Drug Administration (FDA), supposedly due to some fraud or unreliability in the clinical trial data treatment.[38,39] Consequently, the Drugs.com database does not list possible MSR interactions. The Drugbank database lists up to 1423 potential interactions, although there is no indication of their possible respective severity.[40]

It has a very wide receptor activity spectrum, being an antagonist/inverse agonist at histamine H_1, serotonin 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7, adrenergic α_1 and α_2 receptors, and a NRI as well (antagonist of the norepinephrine transporter [NET]).[41] MSR has maximum affinity toward H_1 receptors, and this explains its strong sedative effects; on the contrary, muscarinic affinity is very low, giving the drug a relatively low incidence of cardiovascular side effects.[42]

Recently, it has been found to directly activate κ-opioid receptors, displaying partial agonist activity in different cell systems.[43] It has also demonstrated to significantly lower withdrawal symptoms and duration in medication-supported physical detoxification of opioid-addicted subjects; however, it also increased the dropout rate leading to overall worse results.[44]

The drug is administered as a racemate, although the two enantiomers seem to have significantly different pharmacological activity: *S*-(+)-MSR is about 2 to 300 times more potent than *R*-(−)-MSR as an antidepressant, but the two enantiomers have similar sedative properties.[45]

MSR metabolism includes three main pathways: 8-hydroxylation, *N*-demethylation, and *N*-oxidation (Figure 1B-D). *N*-desmethylMSR and 8-hydroxyMSR retain antidepressant properties but are less sedating than mianserin, while mianserin *N*-oxide seems to be much less active.[43] Koyama et al[46] have determined that 8-hydroxylation of both enantiomers of mianserin is mediated by cytochrome P 450 (CYP) isoform 2D (followed by

2B6, 3A4, and 1A2), while *N*-demethylation of both enantiomers is catalyzed mainly by CYP2B6 (followed by 2C19, 1A2, 3A4, and 2D6). *N*-oxidation is catalyzed mainly by CYP1A2 (and 3A4). CYP3A is involved to a certain extent in each of the stereoselective mianserin pathways. Regarding CYP2D, five CYP2D isoforms (2D1, 2D2, 2D3, 2D4, and 2D6) produce similar levels of 8-hydroxyMSR. CYP2D3 and 2D4 are the most efficient *N*-demethylation agents, while only CYP2D1 produces MSR *N*-oxide (at low levels). 8-Hydroxy-*N*-desmethylMSR is formed by CYP2D4 and 2D6. [47]

CYP2D metabolism is markedly stereoselective, with high specificity towards the *R*-(−) enantiomer: by CYP2D1 and 2D4 for the formation of 8-hydroxyMSR and MSR *N*-oxide, and by CYP2D6 for the formation of *N*-desmethylMSR.[45]

3.1.1 | Mianserin interactions

Clinically relevant data

There is some lack of data from studies on humans regarding MSR interactions. It is known that age, sex, smoking, and coadministration of benzodiazepines do not significantly alter MSR metabolism.[48]

Interaction data from animal studies (low or uncertain clinical significance)

DDIs data comes mostly from animal studies, which are known to be hardly translatable to the clinical setting, especially regarding pharmacokinetic interactions.

Caffeine and sildenafil have been found to increase the effect of MSR in the forced swim[49,50] and tail suspension tests[47]; this interaction is probably not pharmacokinetic in nature, since the brain levels of MSR were not changed by either compound. On the contrary, traxoprodil has no effect in the efficacy of MSR in the forced

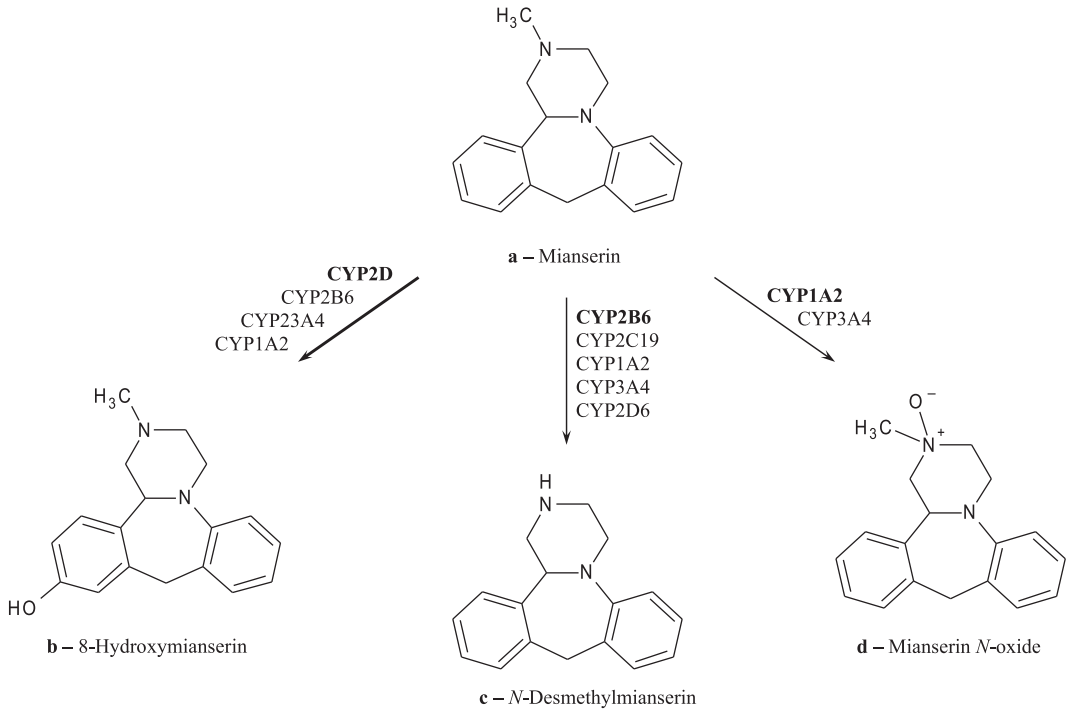


FIGURE 1 Main metabolic pathways of mianserin. CYP, cytochrome P 450

swimming test, despite its capacity to increase the effect of agomelatine by increasing its brain concentration.[51] In rats, although it moderately increases blood pressure, MSR treatment has no effect on the hypotensive effect of propranolol and enalapril, and significantly enhances the effect of prazosin.[52] There is also some clue that MSR could increase the antinociceptive effect of metamizole and indomethacin (but not morphine) in mice.[53]

3.1.2 | Therapeutic drug monitoring

According to the ACNP's TDM guidelines, MSR is a "level 3" drug, that is, its TDM can be used to control whether drug concentrations correspond to reference ranges, for special indications or to solve clinical problems.[31] The reference therapeutic MSR level range at through (C_{min}) is 15 to 70 ng/mL, with a laboratory alert level (risk of toxicity) of 140 ng/mL.[31,54]

Generally, the number of published analytical methods for the TDM of MSR has been declining over the years, probably due to a parallel decline in its use in clinical settings.

Liquid chromatography-tandem mass (LC-MS/MS) is widely used to measure MSR concentrations in plasma or serum,[55] sometimes with *N*-desmethylMSR,[56] or with the *N*-desmethyl, 8-hydroxy, and *N*-oxide metabolites (using a monolithic silica column and solid-phase extraction for sample pretreatment).[57] High performance liquid chromatography-spectrophotometric detection (HPLC-UV) is the most frequent alternative.[58]

A capillary zone electrophoresis (CZE)-UV method has been proposed for the enantioselective analysis of MSR in serum, using 2-hydroxypropyl-β-cyclodextrin as the chiral selector.[59]

A method based on gas chromatography (GC) exists, coupled to surface ionization detection (SID),[60] a type of GC detector particularly suited for the analysis of organic amines.[61]

3.2 | Mirtazapine

Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methylpyrazino2,1[a]pyrido2,3-c2-benzazepine [MRT], Figure 2A) is a recent SGA approved for this indication by FDA in 1996.[62] It is currently also used against anxiety and post-traumatic stress disorder.[63] A recent study[64] suggests that MRT could also be useful in movement impairment, such as Parkinson's disease or akathisia caused by neuroleptic drugs. Chemically, MRT is a piperazinoazepine compound similar to MSR. It belongs to the class of "Noradrenergic and Specific Serotonergic Antidepressants" (NaSSA) and its mechanism of action probably involves the increased release of serotonin and norepinephrine due to the antagonism on autoreceptors and α_2 adrenergic heteroreceptors; MRT also causes 5-HT_2 and 5-HT_3 blockade[65] and H_1 antagonism. MRT seems not to interact with cholinergic receptors and does not inhibit neurotransmitter uptake. This mechanism, which differs from that of most second-generation antidepressants (SGAs), grants good efficacy in the treatment of patients who are nonresponder to the latter[66] and at the same time a faster onset of the therapeutic activity.[67] In fact, when compared with the SGA paroxetine, a SSRI,[68] MRT has shown activity after only a few weeks of administration and better control of anxiety.[65] MRT is available as film-coated Remeron tablets.[69]

MRT is almost totally biotransformed in the liver by action of CYP2D6, 3A4 and 1A2.[70,71] The two main metabolic pathways involve demethylation or oxidation; the most abundant metabolites thus formed are *N*-desmethylMRT (Figure 2B) and 8-hydroxyMRT (Figure 2C).[72] Of these, *N*-desmethylMRT has activity similar to that of the parent drug, but with lower potency[73]; the activity of 8-hydroxyMRT has not yet been completely elucidated. It has been hypothesized that CYP2D6 is responsible for 8-hydroxylation while CYP3A4 is responsible for *N*-demethylation.[74] Seven minor human products of phase I and II metabolism have been reported as well.[75] MRT is a chiral compound and stereospecificity has been found in its biotransformation; the drug, however, is sold as a racemate. The *R*(−)-enantiomer shows the longest elimination half-life from plasma, probably due to the

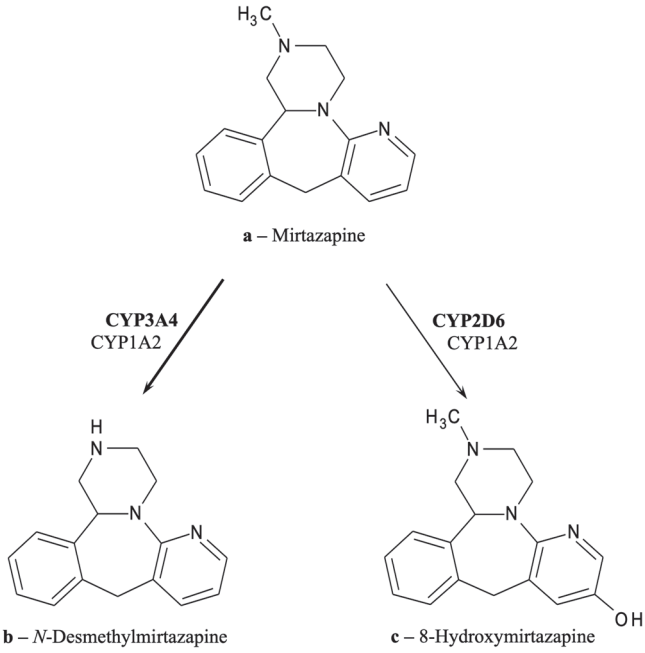


FIGURE 2 Main metabolic pathways of mirtazapine. CYP, cytochrome P 450

formation of a quaternary ammonium glucuronide; the *S*(+)-enantiomer is preferentially metabolized into an 8-hydroxy glucuronide.[70]

Even though MRT has a wider therapeutic index and better tolerability than traditional TCAs,[76] its administration is not devoid of undesired effects. The main side effects of the drug are appetite increase and body weight gain,[77] somnolence and sedation; less frequent are headache, edema, and hepatic enzyme level increase, which can evolve into jaundice and thus require treatment interruption.[78] Recently, there have been reports of a possible increase of suicide risk in adolescents treated with SSRI antidepressants or MRT,[79] though the association is not unequivocal.[80]

3.2.1 | Mirtazapine interactions

Clinically relevant data

MRT does not significantly inhibit or induce the most important CYP subsystems,[72] although it could be considered a weak competitive inhibitor of CYP1A2, CYP2D6, and CYP3A4.[68] Thus, MRT does not seem to have a high potential for pharmacokinetic interactions; it has been verified that it does not interact directly with atypical antipsychotics such as clozapine, risperidone,[81] and olanzapine,[82] nor with antidepressants such as venlafaxine.[83] Nonetheless, a specific form of pharmacodynamic interaction can occur with MAOIs, with abnormal increase of serotonin levels and the onset of serotonin syndrome, including agitation, ataxia, diaphoresis, diarrhea, fever, hyperreflexia, myoclonus, shivering, and changes in mental status.[76] The coadministration of alcohol, anxiolytics, or hypnotics can potentiate the sedative effects of MRT.[76]

Data with low or uncertain clinical relevance, case reports

Single cases of possible interactions with clozapine[84] and risperidone[85] have been reported, causing severe side effects (thromboembolia and rhabdomyolysis). Moreover, MRT augmentation could improve negative and cognitive

symptoms of schizophrenia during risperidone therapy,[86-89] although this has been disputed.[90] The exact mechanism of this possible interaction is still unknown; it could be based on increased activity at serotonergic neurons.[91] Both MRT and other antidepressants (fluoxetine, sertraline, citalopram, and paroxetine) can seldom cause restless legs syndrome (RLS)[92]; episodic findings suggest that combining two of these drugs (viz, MRT and fluoxetine) could sharply increase the frequency of this uncommon side effect.[93] A single case of hyperprolactinemia during polypharmacy with quetiapine and MRT has also been reported.[94] The authors hypothesize that MRT could increase quetiapine-induced D_2-receptor blockade, with subsequent prolactin secretion; alternatively, the well-known agonist action of MRT at opioid μ and κ receptors could modulate D receptor function causing an increase in prolactin release. A single case has been reported of increased prothrombin time during simultaneous intake of MRT and warfarin; the authors have attributed this effect to warfarin metabolism saturation, since CYP3A4 is a common metabolic agent for the two drugs,[95] although the low relative concentrations of the drugs (not close to enzyme saturation) make this explanation unlikely. Similarly, CYP2D6 saturation has been cited as the possible cause of propafenone (an antiarrhythmic) toxicity during simultaneous administration of MRT,[96] with a similar *caveat* regarding the drug concentrations. A double pharmacodynamic and pharmacokinetic interaction can occur between MRT and ondansetron (an antiemetic): both drugs are 5-HT_3 antagonists, however, MRT at antidepressant doses binds to the 5-HT_3 receptor without blocking acute nausea and vomiting, but preventing ondansetron binding.[97,98] A case has been reported of increased levels of both drugs during simultaneous treatment with immunosuppressor tacrolimus and MRT; significant hypotension arose as a consequence.[99]

Interaction data from animal studies (low or uncertain clinical significance)

Studies on lab animals have hypothesized that simultaneous treatment with the antihypertensive prazosin can potentiate the MRT effect of attenuating induction and expression of locomotor sensitization to cocaine.[100] In spontaneously hypertensive rats, MRT administration does not interfere with the hypotensive effects of enalapril or propranolol.[101] A pharmacokinetic interaction can occur between MRT and ritonavir with increased MRT levels, since in mice the latter binds to CYP2D6 with higher affinity than the former.[102]

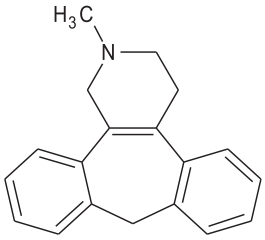
3.2.2 | Therapeutic drug monitoring

According to the most recent AGNP TDM Expert Group consensus guidelines,[31] the TDM of MRT is at "level 2" (recommended), that is, it can be used for dose titration as well as for special indications and problems, and it can increase the likelihood of response in nonresponders. The reference therapeutic MRT level range at through (C_{min}) is 30 to 80 ng/mL, with a laboratory alert level (risk of toxicity) of 160 ng/mL.[31,103]

Several methods can be found in the literature for the determination of therapeutic levels of MRT in serum or plasma.[70,104-114] Most of them also determine the desmethyl metabolite as well as MRT,[105-111] however, only one simultaneously analyses MRT and both main metabolites.[104] Almost all methods are based on HPLC with fluorimetric (FL),[70,102,103,107,108-111] UV,[105,112] or MS[104,105] detection. A CZE-UV[115] and a nano-LC-MS method[116] have also been published for the enantioselective analysis of MRT and its metabolites.[117]

3.3 | Setiptiline

Setiptiline (1,2,3,4-tetrahydro-2-methyl-9*H*-dibenzo(3,4-6,7)cyclohepta(1,2-C)pyridine [STP], Figure 3) is an antidepressant approved in 1989 in Japan, and whose use is mostly limited to this country. It is sold there under the Tecipul brand name. STP acts as a NRI,[118] α_2 receptor antagonist,[119] serotonin (probably 5-HT_2) receptor antagonist and H_1 receptor inverse agonist.[120]



Setiptiline

FIGURE 3 Chemical structure of setiptiline

3.3.1 | Interactions

Clinically relevant data

STP does not seem to significantly alter the activity of CYP (1A2, 2C9, 2C19, 2D6, and 3A4) isoenzymes; it has significant inhibitory activity toward CYP2D6, but it is not clinically significant at therapeutic drug plasma levels.[121]

3.3.2 | Therapeutic drug monitoring

A therapeutic trough plasma level range has not been defined for STP; however, at doses ranging from 0.04 to 0.16 mg/kg, STP produced dose-corrected plasma levels (DCPLs) in the 36.6 ± 18.2 (ng kg)/(mL mg) range. Elder patients (>80 years old) had significantly higher DCPLs.[122]

Due to the drug limited diffusion, analytical methods for the TDM of STP are few and far between, none of them published after the year 2000. All the methods are based on GC, coupled to MS detection after trimethylsilylation to increase the compound volatility,[120] or to SID.[58]

4 | NOREPINEPHRINE REUPTAKE INHIBITORS

4.1 | Reboxetine

The first NRI commercially available for major depression was reboxetine, 2-α-(2-ethoxyphenoxy) phenylmethylmorpholine (RBX, Figure 4A).[123] It is currently marketed in several countries around the world, but not in the USA, as Edronax (UK and Italy), Norebox (Italy), Irenor (Spain), and so forth.[124]

Unlike TCAs, RBX has only minimal sedative and cardiovascular liabilities, probably due to increased pharmacological specificity.[125] Compared with SSRIs, it has demonstrated to cause less sexual dysfunctions and gastrointestinal side effects. [123]

RBX represents a valuable therapeutic tool to investigate the role of NE in depression and in antidepressant therapy and provides a rational alternative for patients resistant to conventional antidepressant therapy (mainly SSRIs).

RBX is primarily metabolized in the liver by CYP3A4, with the formation of *O*-desethylRBX (Figure 4B) as the main metabolite; minor metabolites are two different phenols at the ethoxyphenoxy ring (Figure 4C,D).[126]

RBX possesses two chiral centers and is marketed as the mesylate of the racemic mixture of the (+)-(2*S*,3*S*)- and (−)-(2*R*,3*R*)- enantiomers.[127] In vitro and in vivo receptor binding models suggest that the *S*,*S*-enantiomer is the most potent NRI, although its plasma concentrations are about two times lower than those of the *R*,*R*-enantiomer after administration of the racemate.[128] However, this is evidently not the result of stereoselective metabolism,

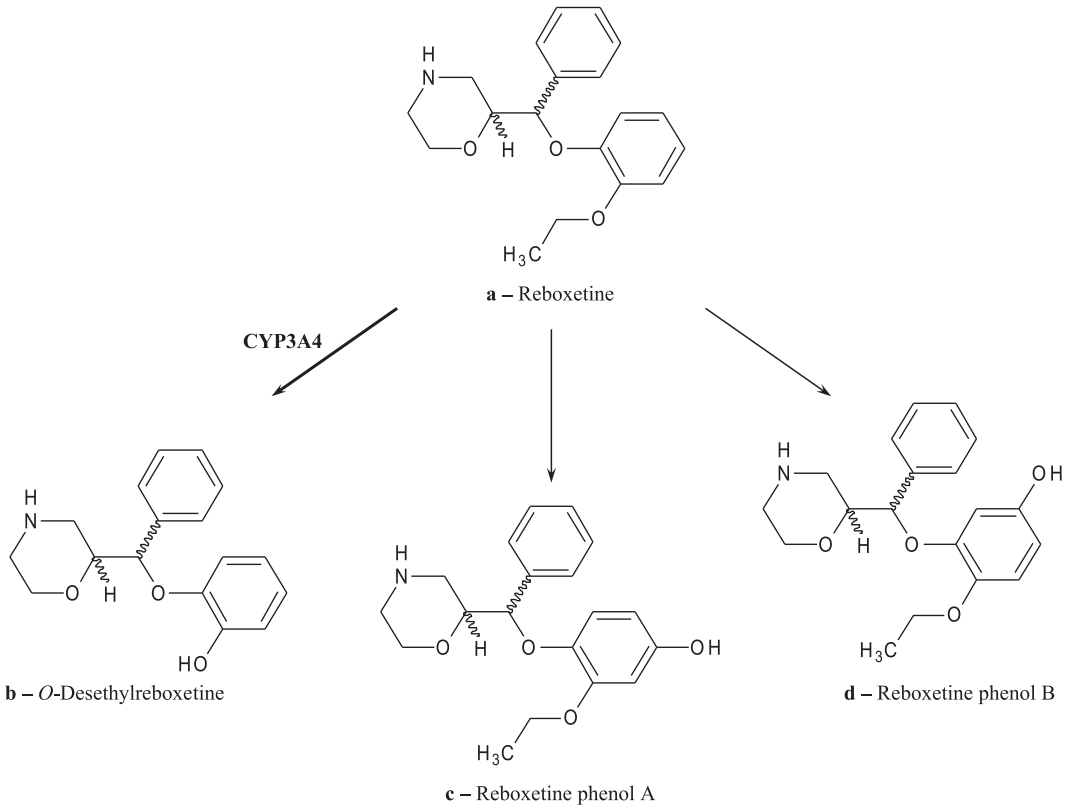


FIGURE 4 Main metabolic pathways of reboxetine. CYP, cytochrome P 450

since both enantiomers are oxidized to approximately the same degree by the cytochrome isoform CYP3A4 in in vitro studies.[129] This is supported by the fact that the enantiomers show similar elimination half-lives, regardless of the route of administration. RBX may be an example of a racemic drug with one clearly active enantiomer, where accurate definition of the dose-effect relationship has been obscured by enantioselective disposition.

4.1.1 | Reboxetine interactions

Clinically relevant data

Due to its NRI activity, RBX reduces several effects of methylenedioxymethamphetamine (MDMA), including excitation, mood elevation, cardiovascular stimulation, and norepinephrine plasma level increase, despite also causing significant MDMA and metabolite level increases.[130] Coadministration of RBX with MRT produced a significant reduction of the cortisol, ACTH, and prolactin secretion stimulation caused by the former; GH secretion patterns remained unchanged. It seems that the stimulatory effects of RBX on pituitary hormone secretion via noradrenergic mechanisms are counteracted in part by the α_2- and cortisol secretion-blocking properties of MRT.[131] Although both RBX enantiomers are known as weak in vitro inhibitors of CYP2D6 and 3A4,[127] in vivo the drug has shown no significant effect on these two CYP isoforms,[132] nor on CYP2C19, 1A2, 2C9, 2D6, 2E1, or 3A4.[124] It has been verified that RBX has no effect on the metabolism of clozapine, risperidone, and their main metabolites.[133]

Data with low or uncertain clinical relevance, case reports

In a preliminary study, RBX at low doses was effective as an augmentation agent in treating depression in SSRI-nonresponder patients. This effect could be due to presynaptic interactions between serotonergic and noradrenergic systems involving presynaptic α_2-adrenergic auto- and heteroreceptors and resulting in the potentiation of the activity of both systems.[134]

Interaction data from animal studies (low or uncertain clinical significance)

In a rat model of seizures, RBX did not affect the anticonvulsant activity of valproate, phenobarbital, ethosuximide, or clonazepam, while also showing some anticonvulsant activity on its own[135]; in the mouse, it did not alter the activity or the brain concentrations of valproate, carbamazepine, phenytoin, or phenobarbital.[136]

4.1.2 | Therapeutic drug monitoring

The most recent AGNP TDM Expert Group consensus guidelines[31] list the TDM of RBX is at "level 3" (useful), that is, it is most useful for special indications and problems. The reference therapeutic RBX level range at through (C_{min}) is 60 to 350 ng/mL, with a laboratory alert level (risk of toxicity) of 300 ng/mL.[31,137]

Several papers are reported in the literature, which determine reboxetine in biological fluids. HPLC-FL has been used for the determination of reboxetine enantiomers in human plasma after derivatization with 9-fluorenylethyl chloroformate[138,139] or with 7-flouro-4-nitrobenzo-2-oxa-1,3-diazole.[140] Other papers have been published, which describe the use of HPLC-UV methods,[135,141,142] and also LC-MS methods for the enantioselective determination of RBX and its *O*-desethylRBX metabolite.[143] A multianalyte method by CG-MS/MS has been published for the determination of reboxetine (as well as fluoxetine, norfluoxetine, and paroxetine) in a miniaturized biological matrix, namely, dried blood spots.[144] Recently, LC-MS/MS[145,146] and ultra-high performance liquid chromatography (UHPLC)-MS/MS[147] have become more common than other techniques. Enantioselective methods[148,149] have also been described and HPLC-UV[150] has been used for the quality control of reboxetine in pharmaceutical formulations.

4.2 | Viloxazine

Viloxazine (2-(2-ethoxyphenoxy)methylmorpholine [VLX], Figure 5A) is a bicyclic methylmorpholine derivative once sold under the tradenames Vivalan, Vicilan, Emovit, and Vivarint. It was introduced during the 1970s and was approved in some European countries. Its commercial success was limited, and it was withdrawn by the manufacturer during the 2000s, probably for its low profitability.[151] Due to its stimulant effect without apparent dependence, some trials to repurpose VLX have been made, and in 2017 it was still under development for possible application to ADHD therapy with the name Catatrol.[152]

Although VLX possesses a stereogenic center and its (*S*)-(−)-isomer is about five times more active than the (*R*)-(+)-isomer,[153] the drug was sold as a racemic mixture.[154] Regarding VLX metabolism, O-dealkylation, the major metabolic pathway in the rat (Figure 5B), is not significant in man and the main compound present in plasma at all times is the parent drug; it seems that no metabolite shows any significant antidepressant activity.[155]

4.2.1 | Viloxazine interactions

Clinically relevant data

VLX is a potent inducer of CYP1A2, but not of CYP2B6 or CYP3A4.[156] For this reason, it could heavily influence the plasma levels of other drugs metabolized by CYP1A2, such as antidepressants (some tricyclics, fluvoxamine,

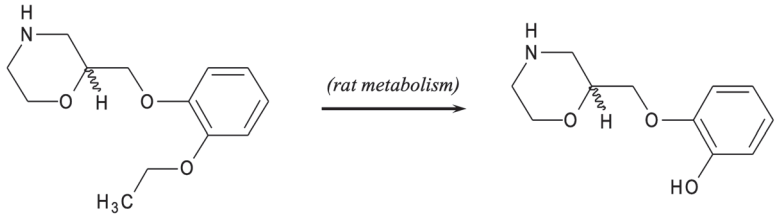


FIGURE 5 Main metabolic pathway of viloxazine

agomelatine, and duloxetine), antipsychotics (clozapine, olanzapine, and haloperidol), xanthines, and some cardiovascular drugs (mexiletine, propranolol, and verapamil).[157]

VLX is known to cause increases in the serum levels of some antiepileptics, such as carbamazepine (by up to 250%)[158] and phenytoin (by about 37%),[159] but not oxcarbazepine.[160] The increase in carbamazepine levels coincides with a dramatic decrease in VLX levels.

Data with low or uncertain clinical relevance, case reports

A case report confirmed that, as shown by clinical studies, VLX increases carbamazepine serum levels.[161]

Interaction data from animal studies (low or uncertain clinical significance)

In rats, VLX prevents the anorectic activity of fenfluramine and tiflorex, but not that of mazindol or amphetamine; this effect has been ascribed to possible 5-HT receptor blockade by the drug.[162]

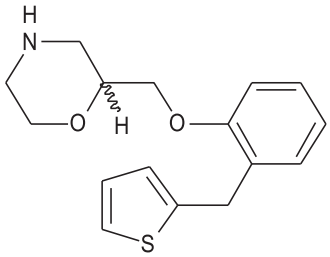
4.2.2 | Therapeutic drug monitoring

Due to its discontinued drug status, VLX is only included in the 2004 edition of the AGNP TDM expert group consensus guidelines[30]; in it, the TDM of VLX is at "level 3" (useful), that is, it is most useful for special indications and problems. The reference therapeutic VLX level range at through (C_{min}) is 20 to 500 ng/mL.[31,163] Cases of intoxication with up to 4 g of the drug have been reported, with only mild CNS symptoms or, in some instances, seizures or extra-pyramidal symptoms.[164]

For the same reason, analytical methods for VLX analysis in biological fluids are not recent; most of them only include VLX for completeness' sake when analyzing toxicological specimens. GC-nitrogen-phosphorus detection (NPD) toxicological methods have been published,[165-167] one of whom includes a performance comparison between different kinds of solid-phase extraction sorbents for sample pretreatment[163]; multianalyte GC-MS methods have been also developed.[168,169] Multianalyte methods including VLX exploit LC-MS/MS,[170] HPLC-UV,[171] or HPLC-photodiode array (PDA) detection[172] to analyze several classes of antidepressants. A voltammetric method has been reportedly applied to VLX analysis in serum.[173]

4.3 | Teniloxazine

Teniloxazine (2-2-(thiophen-2-ylmethyl)phenoxymethylmorpholine [TNX], Figure 6), is a methylmorpholine derivative, similar to VLX in structure (it has a thiophen-2-ylmethyl residue instead of an ethoxy residue). Also known as sufoxazine or sulfoxazine, it is approved as an antidepressant in Japan only, and is sold there as Lucelan or Melatone. It is an NRI, fairly selective over serotonin and dopamine reuptake, and also a 5-HT_{2A} antagonist.[174]



Teniloxazine

FIGURE 6 Chemical structure of teniloxazine

Due to the extremely limited diffusion of this drug, most of its pharmacological characteristics are unclear, and its DDIs have never been studied in depth.

4.3.1 | Therapeutic drug monitoring

No analytical paper in the literature is devoted to the analysis of TNX. A recent (2016) review of analytical methods for the determination of NRI antidepressants in biological fluids, which included explicitly TNX, does not report any analytical method suitable for its TDM.[175] A pharmacokinetic study in healthy subjects and patients suffering from hepatic impairment reports the analytical method used to determine the pharmacokinetic parameters of the drug: it is an HPLC-UV method coupled to sample pretreatment by liquid-liquid extraction.[176] Although no clear therapeutic range for TNX plasma levels has been established, trough plasma levels of 17 to 22 ng/mL have been observed in healthy volunteers at steady state at a 160 mg/day dose.[175]

4.4 | Atomoxetine

Atomoxetine ((3*R*)-*N*-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine [ATM], Figure 7A) is the first nonstimulant drug used in the therapy of ADHD. It is included here, since its mechanism of activity is thought to be similar to that of some antidepressants: the selective reuptake of norepinephrine. It was approved in 2002 in the USA and is currently sold under the *Strattera* brand name and also as a generic drug (oral capsules containing 10-100 mg in both cases).[177] The initial dose for ADHD therapy is 40 mg/day divided in one or two administrations, to be escalated to 80 mg after a few days of therapy, and up to 100 mg/day after 2 to 4 weeks if symptom control is not optimal. ATM also shares with antidepressants the risk of increasing suicidal ideation.[178]

The drug is mainly metabolized in the liver by CYP2D6 to 4'-hydroxyATM (Figure 7B), which is equipotent to the parent drug; the metabolite is then glucuronidated to 4'-hydroxyATM-*O*-glucuronide (Figure 7C), which is inactive.[179] *N*-demethylation (Figure 7D) and benzyl oxidation (Figure 7E) are minor metabolic pathways.[180,181] CYP2C19, 3A, 1A2, 2A6, and 2E1 are also involved in 4'-hydroxyATM formation, but at much slower metabolic rates, while CYP2C19 is the enzyme primarily responsible for the formation of *N*-desmethylATM.[182]

In vitro, in subjects who are poor or intermediate metabolizers for CYP2D6, 4'-hydroxyATM can also be formed by CYP2E1 and CYP3A; in the poorest metabolizers, biotransformation to hydroxymethylATM by CYP2B6 becomes predominant.[183] In pediatric patients, ATM metabolism by CYP2D6 is impaired and an increased production of alternative metabolites (N-desmethylATM and 2-hydroxymethylATM) has been observed in vitro.[180]

4.4.1 | Atomoxetine interactions

Clinically relevant data

As expected from ATM pharmacokinetic profile, any drug which strongly affects CYP2D6 activity has also a potential for DDI with ATM. Fluvoxamine is a moderate CYP2D6 inhibitor and has only a modest effect on ATM plasma levels[184]; the clinical implications are still unclear, but are not expected to be important. The metabolites of the antidepressant, anti-ADHD, anti-obesity, and smoking-cessation drug bupropion, on the contrary, are rather effective CYP2D6 inhibitors, and in fact simultaneous administration of bupropion and ATM cause a five-fold increase in exposure to the latter and a 1.5-fold decrease in exposure to 4-hydroxyATM.[185] Paroxetine, another well-known CYP2D6 inhibitor, has a similar effect.[186,187]

ATM itself does not have strong CYP-inhibiting or CYP-inducing properties; in vivo, at therapeutic levels, it does not alter significantly the plasma levels of CYP2D6 or CYP3A substrates.[188] For example, ATM does not have significant effects on paroxetine plasma levels.[183]

Data with low or uncertain clinical relevance, case reports

A case of DDI possibly due to CYP2D6 inhibition by fluoxetine has been reported.[189] A case of takotsubo cardiomyopathy has been reported during coadministration of ATM and fluoxetine; it is hypothesized that this could be caused by the synergic action of the two drugs on noradrenergic transmission.[190]

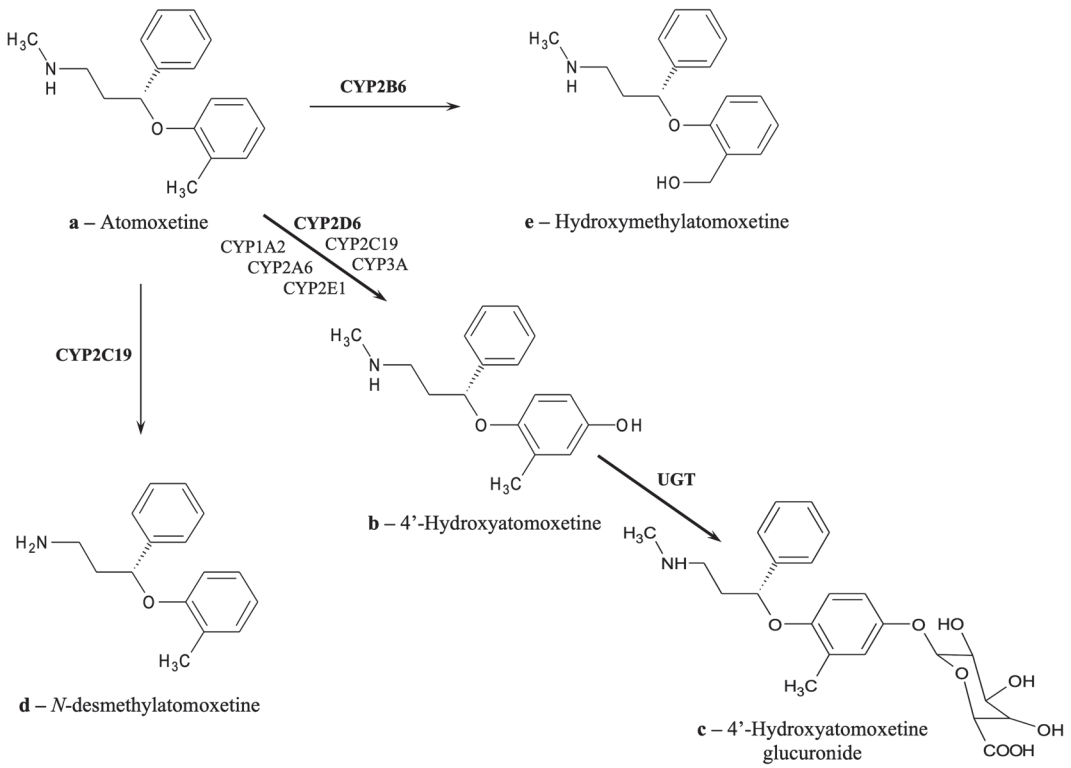


FIGURE 7 Main metabolic pathways of atomoxetine. CYP, cytochrome P 450

4.4.2 | Therapeutic drug monitoring

According to the most recent AGNP TDM Expert Group consensus guidelines,[31] the TDM of ATX is at "level 3" (useful), that is, it is particularly suited for special indications and problems. The reference therapeutic ATX concentration range is reported after 60 to 90 minutes from administration (C_{max}) due to its short half-life, and is 200 to 1000 ng/mL, with a laboratory alert level (risk of toxicity) of 2000 ng/mL.[31,191] Due to the limited use of this drug, analytical methods for ATM analysis in biological fluids are not numerous.

An LC-MS/MS method was applied to the TDM of patients undergoing ATM treatment; this method includes the determination of two ATM metabolites (4-hydroxyATM and *N*-desmethylATM) and has been validated for different biological matrices, including urine, oral fluid, sweat patches,[192] and hair,[193] as well as plasma. Another LC-MS/MS method includes three metabolites: 4-hydroxyATN, *N*-desmethylATM, and 4-hydroxyATM-*O*-glucuronide in plasma and urine.[194] LC-MS/MS was also used for a pharmacokinetic and pharmacodynamic study[195] and for other TDM-like applications.[196] HPLC-FL after derivatization with different reagents has been applied as well for TDM purpose on plasma[197-199] and oral fluid.[193] A few HPLC-UV methods for ATM in plasma are also available.[200,201] GC-MS[202] and GC-NPD (with MS identity confirmation)[203] have been used to quantitate ATM for forensic purposes; of course, possibility of application to TDM is not assured. A single CZE-electrochemiluminescence (ECL) detection method has been published, that includes the drug determination in rat plasma (no metabolite is included).[204]

5 | SEROTONIN, NOREPINEPHRINE, AND DOPAMINE REUPTAKE INHIBITORS

5.1 | Nefazodone

Nefazodone (2-3-4-(3-chlorophenyl)piperazin-1-ylpropyl-5-ethyl-4-(2-phenoxyethyl)-1,2,4-triazol-3-one [NFZ], Figure 8A) is a phenylpiperazine antidepressant, a triazolone analog of the SARI trazodone and also of the antipsychotic aripiprazole. Introduced in 1994, it has now been voluntarily discontinued in many countries (in 2003 in most European countries, but notably not in the USA) due to its increasingly rare use, attributed to competition from other antidepressants and to a worrying side effect, namely, severe and potentially fatal liver toxicity.[205] Due to its complex receptor and transporter interaction profile, NFZ could be inserted in either the SARI or the SNDRI class.

More than 25 NFZ metabolites are currently known,[206] however, just three of these are known to be active: hydroxyNFZ (Figure 8B), triazoledione (Figure 8C), and *m*-chlorophenylpiperazine (mCPP, Figure 8D)[207]; mCPP is a psychoactive substance that can cause hallucinations and is also a metabolite of the SARI antidepressant trazodone.[208] It seems that all of these metabolites are mainly formed in the liver by CYP3A4,[209] while CYP2D6 further transforms mCPP into *p*-hydroxy-mCPP (Figure 8E).[210] Triazoledione is much less active than NFZ but reaches plasma levels up to 10 times higher than its parent drug,[211] so its contribution to the clinical effect is still debated.

5.1.1 | Nefazodone interactions

Clinically relevant data

NFZ is a CYP3A4 inhibitor, as well as a substrate.[212] For this reason, it can cause plasma level increases of drugs biotransformed by CYP3A4, such as the antihistamines loratadine and terfenadine; this interaction can produce clinically significant QT interval prolongation.[213] Significant CYP3A4-mediated metabolism inhibition has been observed also for methylprednisolone.[214] NFZ effects on other CYP3A4 substrates, such as clozapine,[215] are minimal. NFZ does not alter the pharmacokinetics of phenytoin, when the latter is administered in a single dose.[216]

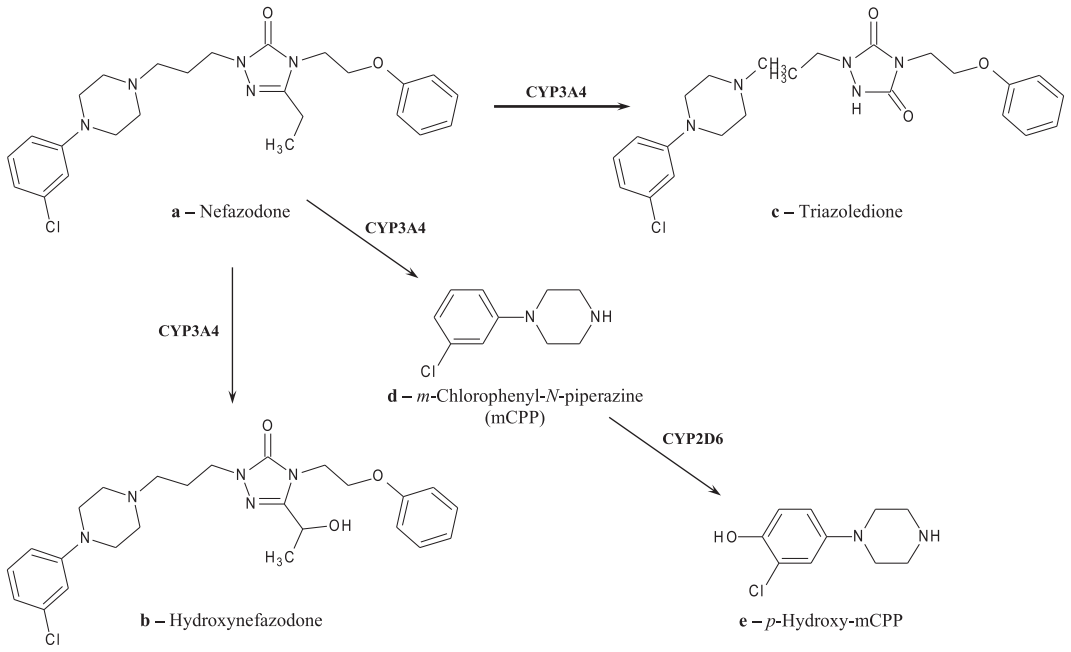


FIGURE 8 Main metabolic pathways of nefazodone. CYP, cytochrome P 450

NFZ can increase the plasma levels of digoxin[217] and haloperidol,[218] although clinical parameters do not seem to be affected by this change; neither drug affects the plasma levels of NFZ. The drug also influences the plasma levels of some benzodiazepines[219] (such as alprazolam,[220] triazolam,[221] midazolam[222]), but not all of them; for example, lorazepam is not affected.[223] No pharmacokinetic interaction between NFZ and desipramine[224] or lithium[225] has been observed.

Data with low or uncertain clinical relevance, case reports

Single cases have been reported of increased plasma/serum levels of several CYP3A4-metabolized drugs during simultaneous NFZ administration: pimozide,[226] sirolimus,[227] triamcinolone,[228] and zopiclone.[229] Peculiar interactions can happen between NFZ and the antiepileptic carbamazepine, which is both a substrate and an inducer of CYP3A4; studies have found increased exposure to carbamazepine[210] and greatly reduced exposure to NFZ during coadministration.[230]

5.1.2 | Therapeutic drug monitoring

No TDM guidelines for NFZ have been published by the AGNP, although the drug is cited in the 2004[30] and 2011 editions of their *Consensus*. However, other sources[231] suggest that TDM research could be useful for NFZ due to its nonlinear kinetics and the presence of active metabolites. At a 600 mg/day (therapeutic) dose, patients had NFZ plasma levels in the 400 to 1000 ng/mL range, with the main metabolites at 180 to 350 ng/mL (hydroxyNFZ) and 40 to 55 ng/mL (*m*-CPP).[232]

Most published methods for NFZ determination in plasma/serum also include the three active metabolites. A high-throughput LC-MS/MS method with direct-injection on-line extraction has been published for this purpose[233]; other LC-MS/MS methods also exist.[226,234]

Older papers reported the use of HPLC-UV[235-237] and HPLC-electrochemical (EC) coulometric detection[238] for NFZ analysis, and include the drug determination in breast milk[230] as well as plasma/serum.

6 | MELATONERGIC AGONISTS AND SELECTIVE SEROTONERGIC ANTAGONISTS

6.1 | Agomelatine

Agomelatine (*N*-2-(7-methoxynaphthalen-1-yl)ethylacetamide [AGT], Figure 9A), the naphthalene analog of melatonin, is currently thought to act through melatonergic MT_1 and MT_2 receptor agonism and serotonergic 5-HT_{2B} and 5-HT_{2C} receptor antagonism.[239] It does not seem to possess relevant affinity for monoamine transporters, nor for adrenergic, cholinergic, or dopaminergic receptors.[240]

It has been approved in the EU and Australia between 2009 and 2010 and is sold under the names Valdoxan or Thymanax.[241] It has never been approved in the USA, and its approval procedure has been stopped in 2011[242] due to the unsatisfactory results of a clinical study. Hepatic toxicity of AGT is a concern and has led to a postauthorization opinion by the European Medicines Agency (EMA) with new contraindications.[243]

AGT bioavailability is low, about 5%, due to massive first-pass metabolism,[244] and biotransformation is effected mainly by CYP1A2, with a small contribution by CYP2C9/19.[245] The most important metabolites thus formed are 3-hydroxyAGT (by CYP1A2; Figure 9B) and *O*-desmethylAGT (by CYP2C9; Figure 9C); both metabolites are inactive and can be further metabolized to 3-hydroxy-*O*-desmethylAGT (Figure 9D).[246] Other metabolic pathways have been recently reported.[247]

6.1.1 | Agomelatine interactions

Clinically relevant data

Drugs that interact with CYP1A2 may dramatically change the plasma concentrations of AGT.[248] Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor, markedly inhibits the metabolism of agomelatine, resulting in a 60-fold increase of AGT exposure. Combination of AGT with estrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure to AGT, although in trials this did not cause clinically significant effects.[249] Smoking induces CYP1A2 and has been shown to decrease the bioavailability of AGT.[250]

Conversely, AGT does not seem to significantly induce any CYP450 isoenzyme.[245]

Data with low or uncertain clinical relevance, case reports

A case of hyperhidrosis[251] and one of akathisia[252] have been reported during coadministration of AGT with the SNRI antidepressant duloxetine. Both have been attributed to a pharmacodynamic DDI with excessive noradrenergic stimulation.

Interaction data from animal studies (low or uncertain clinical significance)

In the mouse depression model, caffeine potentiates the effects of AGT without changing its plasma levels.[47] In a mouse depression model, hesperidin (a glycoside typical of *Citrus* fruits)[253] has been found to potentiate the antidepressant effect of AGT.[254]

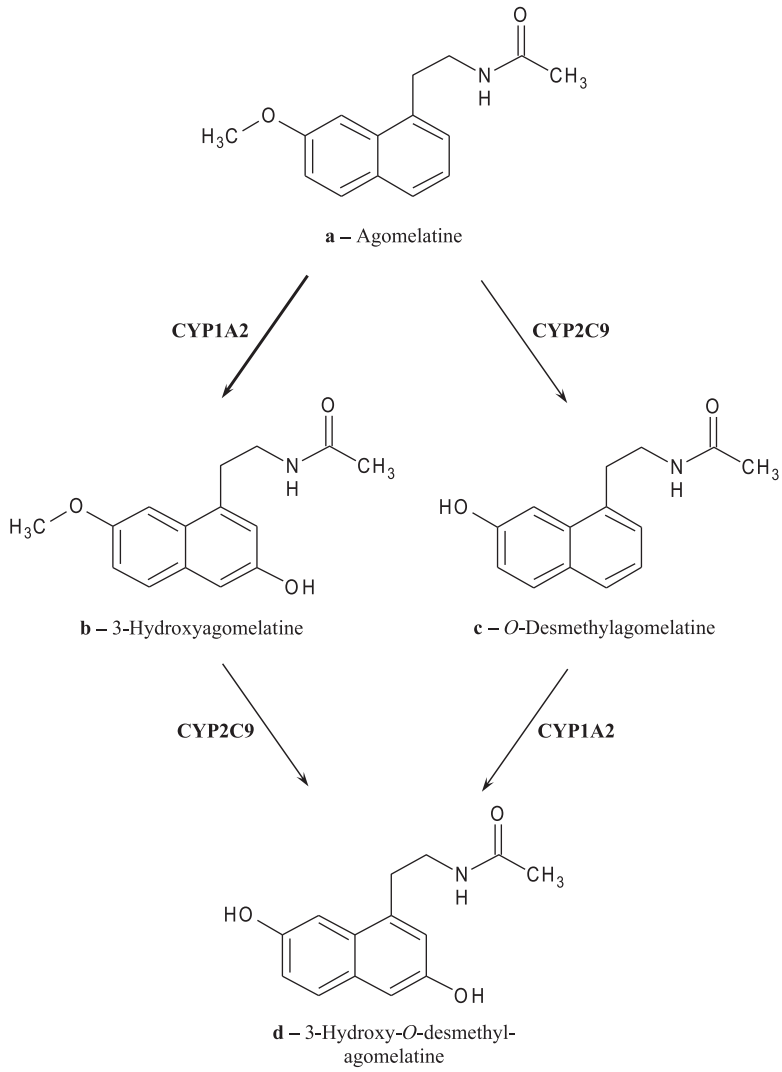


FIGURE 9 Main metabolic pathways of agomelatine. CYP, cytochrome P 450

6.1.2 | Therapeutic drug monitoring

The most recent AGNP TDM expert group consensus guidelines[31] recommend the TDM of AGT at "level 4" (potentially useful), that is, it should be restricted to special cases due to apparent lack of correlation between plasma levels and activity. However, TDM in a research setting could be useful to further investigate this phenomenon, as well as for many other purposes, such as compliance control, DDI monitoring, and so forth. The reference therapeutic AGT level range is reported after 1 to 2 hours (C_{max}), due to its rapid elimination. The range is 7 to 300 ng/mL, with a laboratory alert level (risk of toxicity) of 600 ng/mL (again, after 1-2 hours).[31,255]

Due to the recent introduction of AGT, the most frequently used methods for its TDM are LC-MS/MS[256-260] or UHPLC-MS/MS[261] ones. An LC-MS/MS method includes the determination of the two major metabolites.[262]

A multi-matrix (oral fluid, plasma, whole blood) method based on HPLC-FL has been also published.[263]

7 | NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITORS

7.1 | Bupropion

Bupropion or amfebutamone (2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one [BPR], Figure 10) is a phenylethylamine used for the treatment of depression, also in association with other antidepressants for nonresponder patients, and as a support to smoking cessation or obesity therapy.[264] Its antidepressant activity is thought to be due to norepinephrine and dopamine reuptake, while its antagonism at nicotinic acetylcholine receptors explains its usefulness during smoking cessation therapy.[265]

BPR is available under the brand names Wellbutrin and Zyban. It has been approved for depression during the 1980s in the USA; it was discontinued due to excessive incidence of seizures and then recommercialized at reduced doses.[266]

BPR is administered as a racemate but undergoes significantly stereoselective metabolism: (*R*)-bupropion concentrations are higher than (*S*)-bupropion ones.[267]

The biotransformation of BPR is mediated principally by CYP2B6, producing hydroxyBPR (which can then undergo spontaneous cyclization to the corresponding hemiketals, Figure 10B,C); reduction of the carbonyl group to alcohol by carbonyl reductases generates erythrohydroBPR (Figure 10D) and threohydroBPR (Figure 10E).[268] These metabolites are active, and threohydroBPR and (*R*)-hydroxyBPR reach plasma levels much higher than those of the parent drug, thus they are supposed to contribute significantly to the overall therapeutic effect.[269] Recently, three new metabolites have been discovered: 4′-hydroxyBPR (Figure 10F), and the respective erythro- and threo- 4′-hydroxyhydroBPR (Figure 10G,H); together, these metabolites are excreted in amounts similar to those of all the previously known metabolites.[270]

7.1.1 | Bupropion interactions

Clinically relevant data

Since the main BPR metabolic pathway involves CYP2B6, its inhibition can produce drug level increases; the SSRIs paroxetine, fluvoxamine, sertraline, norfluoxetine (the main fluoxetine metabolite),[271] and venlafaxine[272] are all capable of inhibiting CYP2B6. Some MAOI antidepressants are also CYP2B6 inhibitors, however, their effect seems to be weak; phenelzine could have an impact on BPR levels, but the likelihood of significant clinical implications is low.[273] The main BPR metabolites are CYP2D6 inhibitors; hydroxyBPR possesses the highest inhibitory activity, followed by the other metabolites and finally by the parent drug. They seem even able to downregulate CYP2D6 expression.[274] Thus, complex pharmacokinetic DDI patterns can appear when administering BPR with other drugs metabolized by CYP2D6. The clinical DDIs between bupropion and the CYP2D6-metabolized drugs desipramine and ATX[182] result in marked (up to five-fold) increases in exposure to both victim drugs.[275] Among anticonvulsants, carbamazepine can decrease exposure to BPR while increasing hydroxyBPR concentrations; BPR can increase valproate levels in humans.[276] Tobacco smoking does not affect the plasma levels of BPR. [277]

Data with low or uncertain clinical relevance, case reports

The antiretrovirals ritonavir, efavirenz, and nelfinavir are significant CYP2B6 inhibitors, thus they have the potential for significant pharmacokinetic interaction with BPR.[278] Some cases have been reported of interactions between BPR and drugs metabolized by CYP2D6, such as venlafaxine, bufuralol, tolterodine, metoprolol,[279] imipramine,[280] nortriptyline,[281] and dextromethorphan.[262] Episodic reports of interactions between BPR and alcohol have also been published, with increased aggressiveness as the main symptom.[282] The pharmacodynamic interaction between BPR and pseudoephedrine has been reported to cause potentially fatal cardiovascular effects in the perioperative setting.[283] Simultaneous intake of BPR and MDMA (ecstasy) can increase the plasma

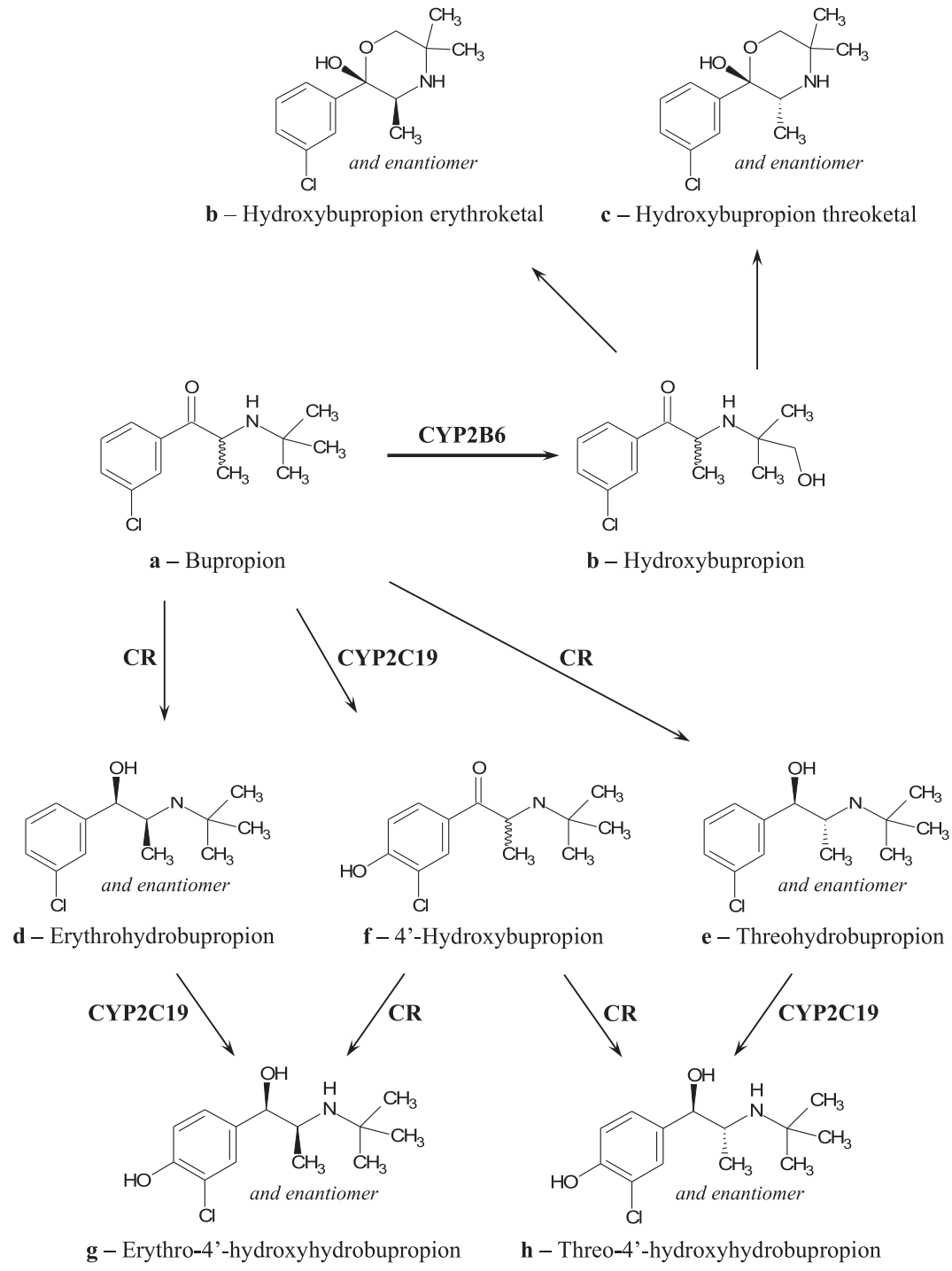


FIGURE 10 Main metabolic pathways of bupropion. CR, carbonyl reductase; CYP, cytochrome P 450

concentrations of both drugs, with enhanced mood effects but decreased cardiovascular effects.[284] A single case report of decreased cyclosporine levels during polypharmacy with BPR has been also published.[285]

Interaction data from animal studies (low or uncertain clinical significance)

Another CYP2B6 inhibitor, with effects on BPR plasma levels in animals, is ticlopidine.[286]

In mice, CYP2D6 inhibition by BPR causes significant increases in risperidone plasma levels.[287] BPR can increase phenytoin levels in the rat.[288] Multiple BPR doses can significantly decrease exposure to digoxin in monkeys, by increasing its renal clearance,[289] probably by means of organic anion-transporting polypeptide 4C1 (OATPC4C1).[290] In rats, BPR can increase the plasma levels of carvedilol[291] and nebivolol.[292]

7.1.2 | Therapeutic drug monitoring

The 2017 AGNP TDM expert group consensus guidelines[31] suggest carrying out the simultaneous TDM of BPR and hydroxyBPR, with a recommendation equal to "level 2" (recommended), that is, there are reliable chemical-clinical correlations and TDM application could significantly increase the therapy success rate. For BPR therapy, the reference therapeutic level range at through (C_{min}) refers mainly to hydroxyBPR; it is 850 to 1500 ng/mL, with a laboratory alert level (risk of toxicity) of 2000 ng/mL.[31,293]

Recently, several LC-MS/MS methods have been developed for the TDM of BPR[294]; most of them include at least the main metabolite hydroxyBPR,[295,296] and some of them include more than one metabolite, usually erythrohydroBPR and threohydroBPR.[297-299] Of course, due to the complex stereoselective metabolism of BPR, chiral LC-MS/MS methods are also available,[300] sometimes also including glucuronidated metabolites.[301] HPLC-UV (in papers published before 2010), [302,303] HPLC-FL after derivatization,[304] and turbulent flow chromatography (TFC)-MS/MS[305] are also represented.

Potentially useful for TDM of pregnant women is the determination of the drug and its main metabolites in umbilical cord plasma and placental tissue.[306]

8 | OTHERS

8.1 | Esketamine

Esketamine ((2*S*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one [ESK], Figure 11A) is the *S*-enantiomer of the well-known general anesthetic ketamine, which is also a relatively common drug of abuse; compared with the racemate, ESK is less prone to psychotomimetic side effects, such as derealization and hallucinations.[307] ESK is available as a nasal spray and an intravenous injectable solution under the brand names Ketanest and Spravato and is currently used as an adjunct to other antidepressants for treatment-resistant depression.[308] As of 2017, it has been approved in several single EU countries (but not by the EU's EMA)[309] and in 2019 has obtained a marketing authorization from the US's FDA.[310] Its main advantage would be the very fast onset of the antidepressant effect, which could be obtained in many cases in a matter of hours, not weeks as happens with almost all other known antidepressant agents (racemic ketamine has a similarly fast onset of action but is not approved as an antidepressant).[311]

The main antidepressant mechanism of ESK is currently believed to be its antagonism at NMDA glutamatergic receptors; however, the drug has also strong affinity toward AMPA glutamatergic and opioid receptors. [312]

The main metabolite of ESK is norESK (Figure 11B), which seems to be produced by action of CYP2B6 and 3A4; however, CYP2C9 and 2C19 could also be involved to a lesser extent.[313] NorESK appears to have significant

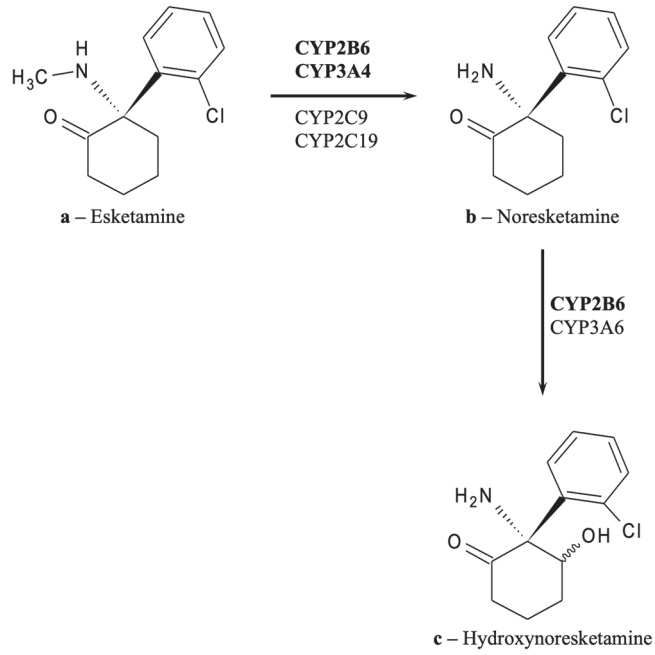


FIGURE 11 Main metabolic pathways of esketamine. CYP, cytochrome P 450

antidepressant activity[314] and reaches plasma levels that can be up to 16 times those of the parent drug.[315] This main metabolite is further metabolized to hydroxynorESK (Figure 11C).[306]

8.1.1 | Esketamine interactions

Clinically relevant data

As expected, the CYP2B6 inhibitor ticlopidine (clinically used as a platelet aggregation inhibitor) can cause significant increases in ESK plasma levels.[316]

Data with low or uncertain clinical relevance, case reports

The herbal antidepressant St. John's wort (*Hypericum perforatum*), a CYP3A4 inducer, strongly decreases exposure to oral ESK and norESK in terms of AUC and C_{max}.[317] However, since ESK is administered parenterally during antidepressant therapy, the significance of this observation is unclear.

Interaction data from animal studies (low or uncertain clinical significance)

In animal studies, ESK itself has inhibitory effects on CYP2C and 3A, and slight inducing effects on CYP1A2.[318]

8.1.2 | Therapeutic drug monitoring

Obviously, when monitoring ESK in patients, chiral methods are required to discriminate between ESK and its enantiomer; nonselective methods used for racemic ketamine are not adequate. No reliable therapeutic plasma concentration range has been established yet for ESK in depression. However, clinical trials have found a mean maximum ESK plasma level (C_{max}) of about 150 ng/mL after a single 84-mg intranasal dose (the maximum suggested dose).[319]

An LC-MS/MS method that includes norESK is available.[320] An enantioselective supercritical fluid chromatography (SFC)-MS method has been published for the monitoring of both ketamine enantiomers in human urine, and it could have interesting application also in TDM. It has the noteworthy advantage of including the enantiomers of three metabolites: norketamine, dehydronorketamine, and (*R*,*R*)-, (*S*,*S*)-hydroxynorketamine.[321]

8.2 | Tianeptine

Tianeptine (7-(3-chloro-6-methyl-5,5-dioxo-11H-benzoc2,1benzothiazepin-11-yl)aminoheptanoic acid [TNP], Figure 12A) is an "atypical" TCA with a benzothiazepine structure, also active against anxious symptoms. It is sold under the brand names Stablon and Coaxil in the EU and in other countries around the world, but notably not in most English-speaking countries (USA, UK, Canada, Australia, and New Zealand). Differently from "traditional" TCAs, which are nonselective inhibitors of serotonin and norepinephrine reuptake, TNP seems to act as a functionally selective μ opioid receptor agonist.[322] Although the exact mechanism of activity has not been exactly determined, other, less accredited theories include serotonin reuptake enhancement[323] and inhibition of glutamatergic transmission.[324]

TNP metabolism occurs by β-oxidation of the acid side chain,[325] and its major metabolites are its pentanoic acid (Figure 12B) and propionic acid (Figure 12C) derivatives; the former has significant antidepressant activity.[326]

8.2.1 | Tianeptine interactions

Clinically relevant data

No pharmacokinetic or pharmacodynamic interaction seems to occur between TNP and oxazepam.[327] Coadministration with alcohol can decrease TNP absorption rate and plasma levels by about 30% but does not affect those of the pentanoic acid metabolite.[328] Clinically, this interaction does not seem to be important.

Data with low or uncertain clinical relevance, case reports

Among cyamemazine, levomepromazine, flunitrazepam, oxazepam, diclofenac, and salicylic acid, only the last drug is able to displace TNP from plasma protein binding (which is normally about 95%), potentially increasing its effects.[329]

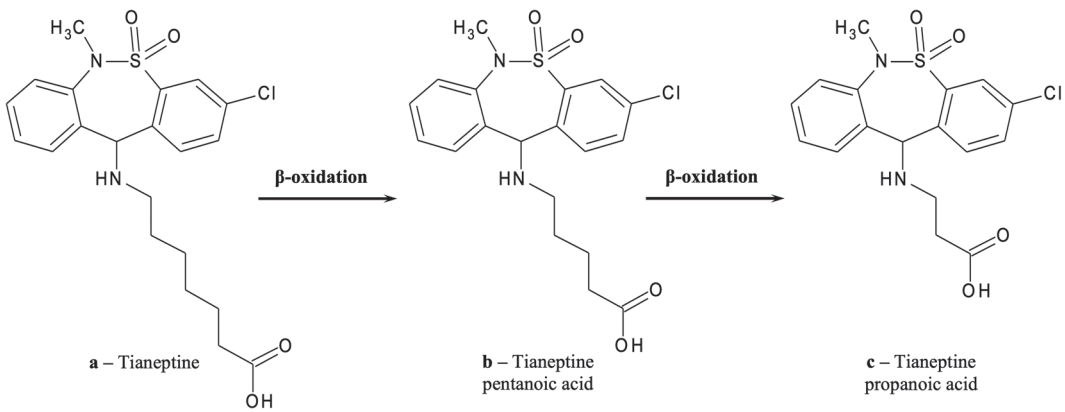


FIGURE 12 Main metabolic pathway of tianeptine. CYP, cytochrome P 450

Interaction data from animal studies (low or uncertain clinical significance)

In the mouse model of epilepsy, TNP enhanced the anticonvulsant action of valproate and carbamazepine, but not that of phenytoin, without altering the brain concentrations of any of these drugs. On the other hand, TNP decreased the brain concentration of phenobarbital, but enhanced its anticonvulsant activity.[330] In mice, sildenafil enhances the activity of TNP, probably by increasing its brain concentration.[48]

8.2.2 | Therapeutic drug monitoring

TNP is present in the most recent AGNP TDM expert group consensus guidelines,[31] and its TDM is listed at "level 3" (useful), that is, chemical-clinical correlations are tentative and TDM is most useful in particular cases. The reference therapeutic TNP level range at through (C_{min}) is 30 to 80 ng/mL, with a laboratory alert level (risk of toxicity) of 160 ng/mL.[31,331]

As usual for drugs not approved in the USA and other English-speaking countries, published analytical methods for TNP in human biological fluids are few and far between.

A recent method for TNP TDM exploits LC-MS/MS and includes the determination of its main active pentanoic acid metabolite[332]; another one carries out the determination of TNP alone.[333] Oher methods include HPLC-FL after derivatization[334] and HPLC-PDA (with simultaneous determination of the pentanoic acid metabolite).[335]

An old ion-pair LC-UV method is also available for the analysis of TNP and the two main metabolites in plasma, urine and solid tissues.[336]

9 | CONCLUSION

The sheer number of different antidepressant classes underscores the intrinsic complexity of MDD treatment, its inherent need for therapy personalization and the current state of incomplete satisfaction with the therapeutic results obtained in a significant number of patients. Despite the many breakthroughs and promises of "magic bullets" against MDD that have appeared over the years, the reality is that MDD is still an undertreated illness, one that continues to cause thousands of deaths and a large amount of suffering and disability all over the world.[337]

Although NGAs have generally obtained a higher level of safety in comparison with TCAs and MAOIs, efficacy is still comparable with that of classical antidepressants. None of the currently available antidepressant classes can be deemed objectively "better" than all the others.[338] While this fact is a witness of incomplete success, it is also proof that each psychiatrist can choose among a wide range of drugs to find the one that best suits the specific needs of each patient. Such a complex and protean disorder as MDD could conceivably never find a single optimal therapeutic agent; however, every effort should be made to tailor the therapy by means of evidence-based optimization and personalization. For this purpose, one of the most interesting options is TDM, which provides objective tools to base clinical decisions upon. Newer and less-used SGAs would particularly benefit from TDM, which would produce data useful to fully understand their chemical-clinical correlations.

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CONFLICTS OF INTEREST

Prof. Serretti is or has been consultant/speaker for: Abbott, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. All other authors declare that there are no conflicts of interest.

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