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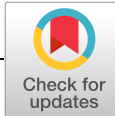
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New-generation, non-SSRI antidepressants: Drug-drug interactions and therapeutic drug monitoring. Part 2: NaSSAs, NRIs, SNDRI, MASSAs, NDRI, and others

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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

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 (SNDRI); melatonergic agonists and selective serotonergic antagonists (MASSAs); and norepinephrine and dopamine reuptake inhibitors (NDRI). 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 MDD¹³; 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 antipsychotics²²⁻²⁵ 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 antidepressant²⁹ 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 NDRI 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: Scopus³⁵ 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 or 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 H₁, serotonin 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, 5-HT₆, and 5-HT₇, adrenergic α₁ and α₂ receptors, and a NRI as well (antagonist of the norepinephrine transporter [NET]).⁴¹ MSR has maximum affinity toward H₁ 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: 5-(+)-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 al⁴⁶ 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-hydroxymianserin. 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-hydroxymianserin 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 tests⁴⁷; 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

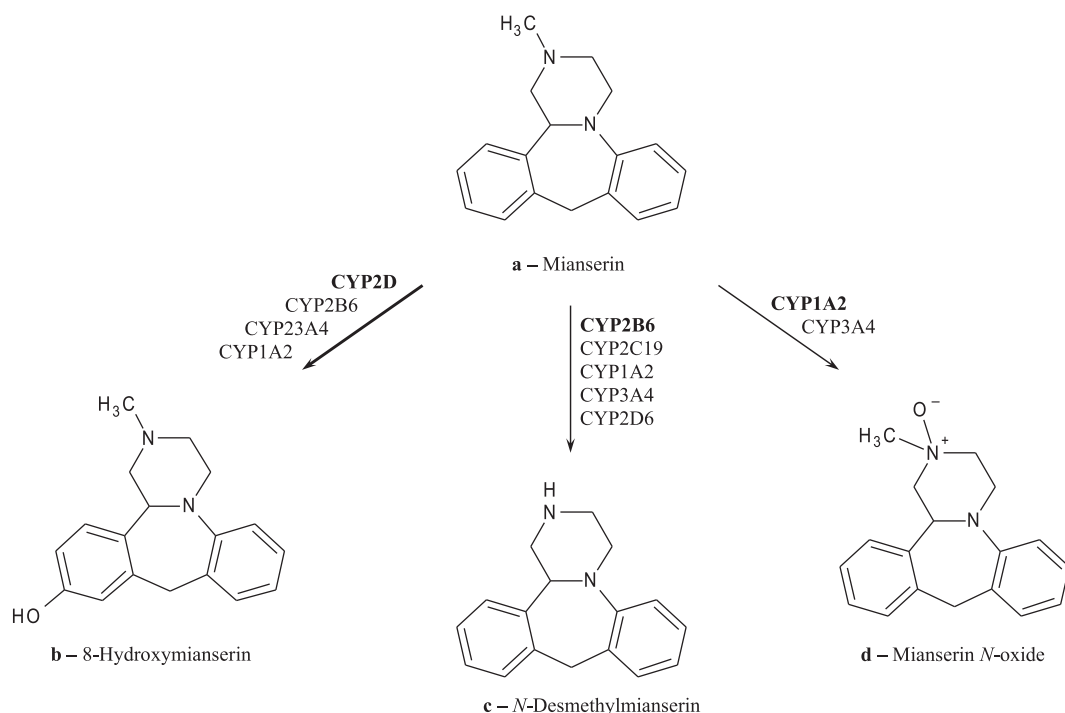


FIGURE 1 Main metabolic pathways of mianserin. CYP, cytochrome P 450

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 trough (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 study⁶⁴ 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-HT₂ and 5-HT₃ blockade⁶⁵ and H₁ 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 latter⁶⁶ 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 potency⁷³; 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

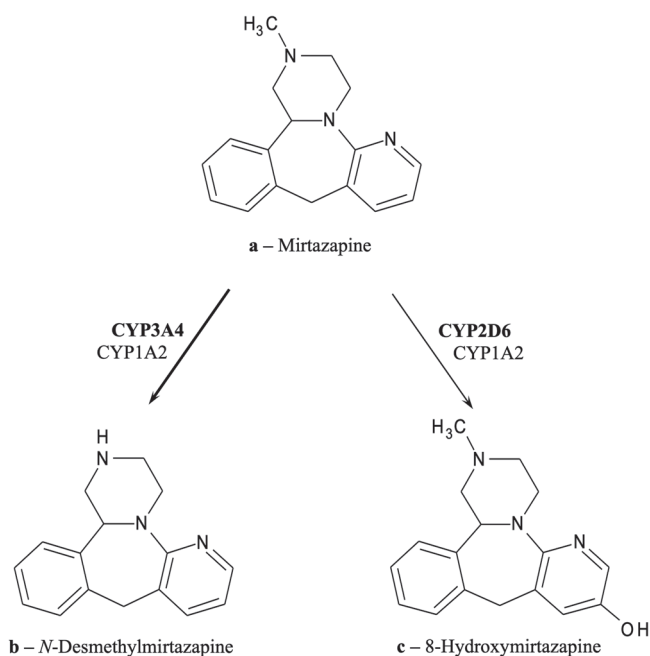


FIGURE 2 Main metabolic pathways of mirtazapine. CYP, cytochrome P 450

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 clozapine⁸⁴ and risperidone⁸⁵ have been reported, causing severe side effects (thromboembolism 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 D₂-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-HT₃ antagonists, however, MRT at antidepressant doses binds to the 5-HT₃ 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

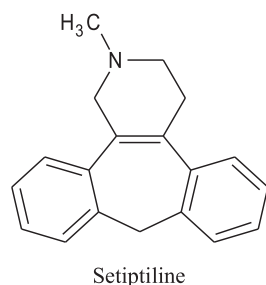
3.2.2 | Therapeutic drug monitoring

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-UV¹¹⁵ and a nano-LC-MS method¹¹⁶ 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-9H-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-HT₂) receptor antagonist and H₁ receptor inverse agonist.¹²⁰

**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 (+)-(2S,3S)- and (-)-(2R,3R)- 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,

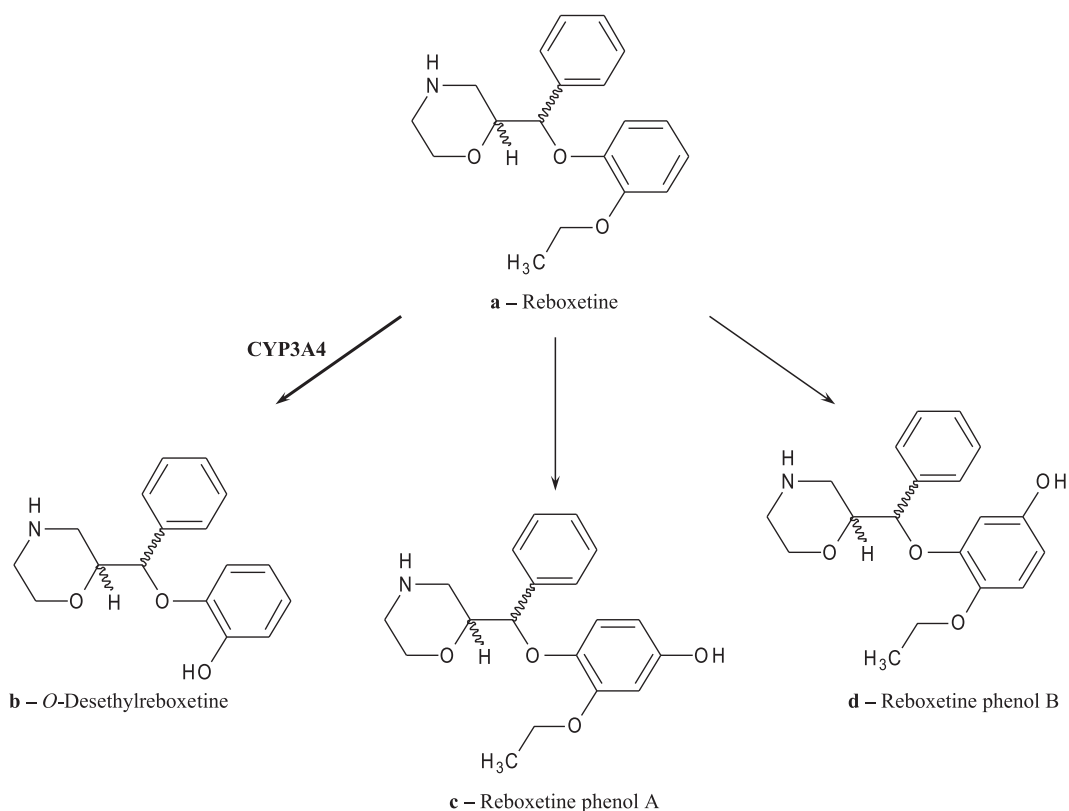


FIGURE 4 Main metabolic pathways of reboxetine. CYP, cytochrome P 450

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 own¹³⁵; 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 guidelines³¹ 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 trough (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-fluorenyl ethyl chloroformate^{138,139} or with 7-fluoro-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/MS¹⁴⁷ have become more common than other techniques. Enantioselective methods^{148,149} have also been described and HPLC-UV¹⁵⁰ 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,

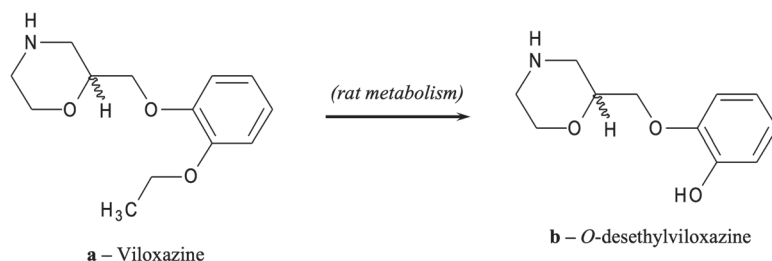


FIGURE 5 Main metabolic pathway of viloxazine

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

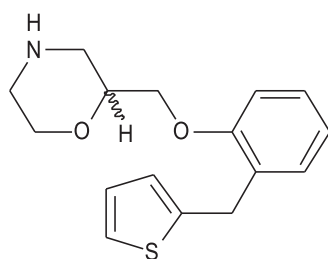
4.2.2 | Therapeutic drug monitoring

Due to its discontinued drug status, VLX is only included in the 2004 edition of the AGNP TDM expert group consensus guidelines³⁰; 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 trough (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 pretreatment¹⁶³; 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) detection¹⁷² 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)phenoxy)methylmorpholine [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 ((3R)-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 levels¹⁸⁴; 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

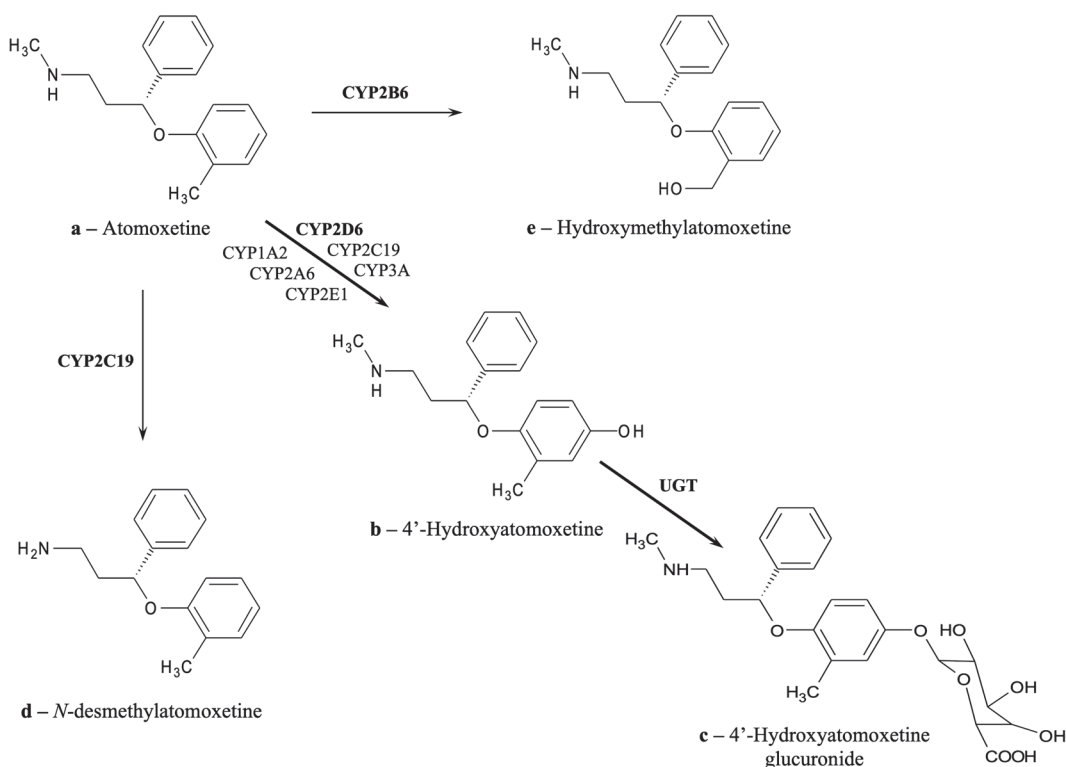


FIGURE 7 Main metabolic pathways of atomoxetine. CYP, cytochrome P 450

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 study¹⁹⁵ and for other TDM-like applications.¹⁹⁶ HPLC-FL after derivatization with different reagents has been applied as well for TDM purpose on plasma¹⁹⁷⁻¹⁹⁹ and oral fluid.¹⁹³ A few HPLC-UV methods for ATM in plasma are also available.^{200,201} GC-MS²⁰² 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

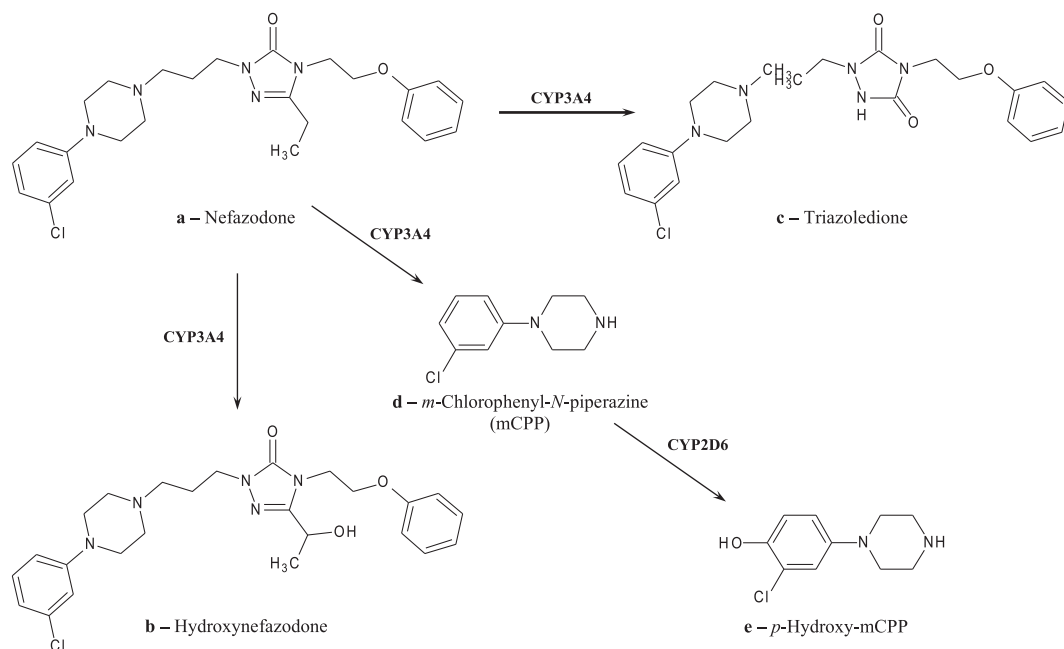


FIGURE 8 Main metabolic pathways of nefazodone. CYP, cytochrome P 450

NFZ can increase the plasma levels of digoxin²¹⁷ 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 benzodiazepines²¹⁹ (such as alprazolam,²²⁰ triazolam,²²¹ midazolam²²²), but not all of them; for example, lorazepam is not affected.²²³ No pharmacokinetic interaction between NFZ and desipramine²²⁴ or lithium²²⁵ 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: pimozi,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 carbamazepine²¹⁰ 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 2004³⁰ and 2011 editions of their *Consensus*. However, other sources²³¹ 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 purpose²³³; other LC-MS/MS methods also exist.^{226,234}

Older papers reported the use of HPLC-UV²³⁵⁻²³⁷ and HPLC-electrochemical (EC) coulometric detection²³⁸ for NFZ analysis, and include the drug determination in breast milk²³⁰ 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 MT₁ and MT₂ 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 2011²⁴² 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 hyperhidrosis²⁵¹ and one of akathisia²⁵² 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

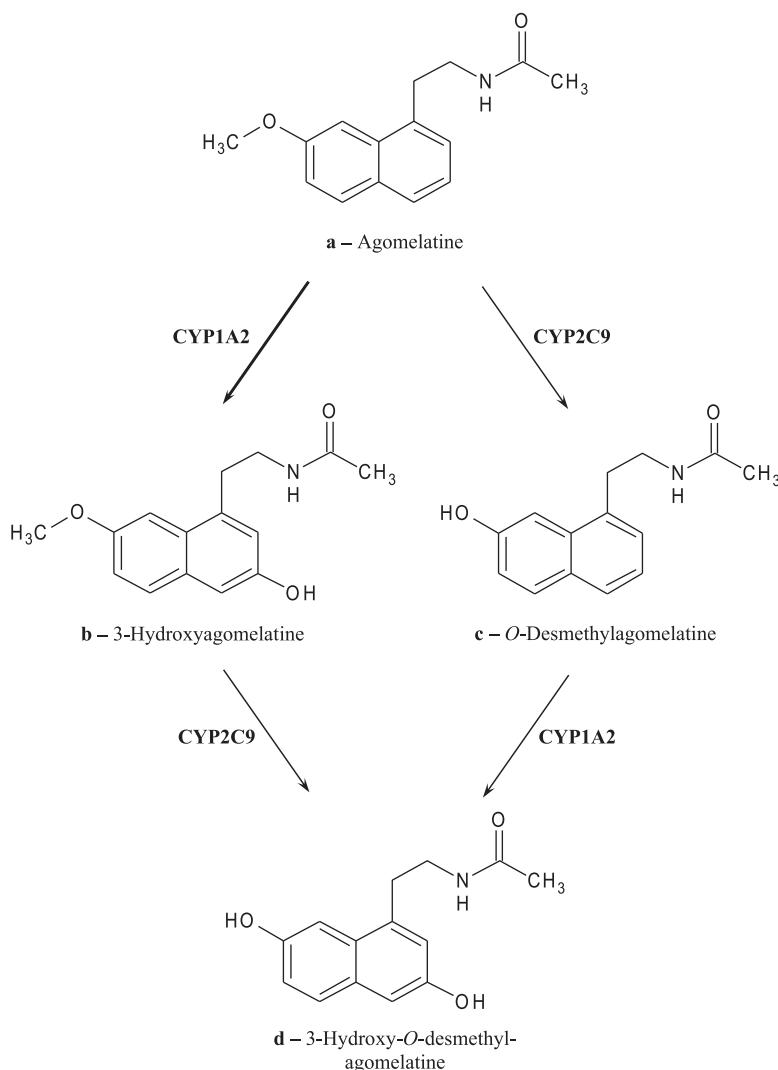


FIGURE 9 Main metabolic pathways of agomelatine. CYP, cytochrome P 450

6.1.2 | Therapeutic drug monitoring

The most recent AGNP TDM expert group consensus guidelines³¹ 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/MS²⁶¹ 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 venlafaxine²⁷² 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 ATX¹⁸² 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, bupropion, 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

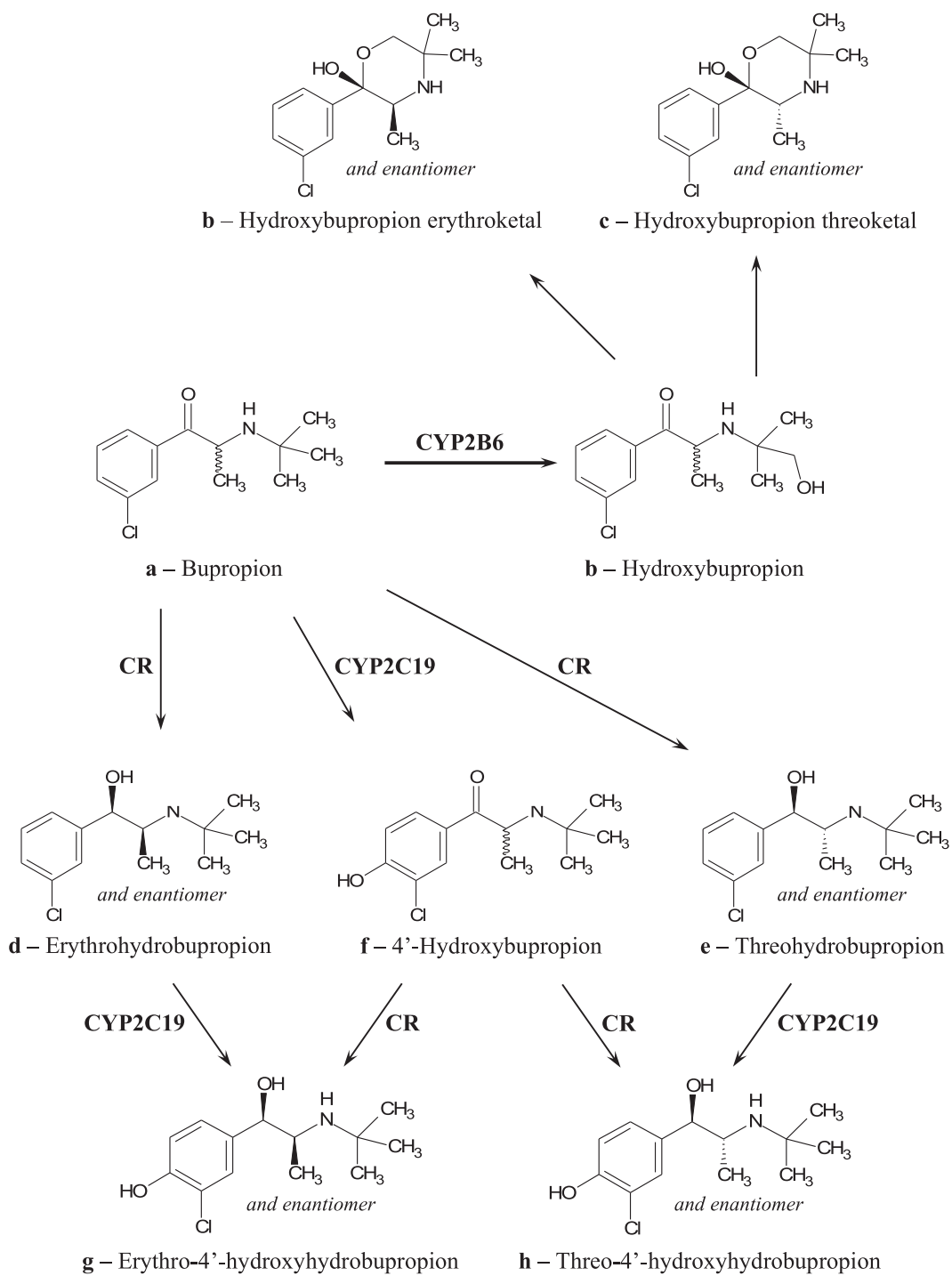


FIGURE 10 Main metabolic pathways of bupropion. CR, carbonyl reductase; CYP, cytochrome P 450

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 carvedilol²⁹¹ and nebivolol.²⁹²

7.1.2 | Therapeutic drug monitoring

The 2017 AGNP TDM expert group consensus guidelines³¹ 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 trough (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 BPR²⁹⁴; most of them include at least the main metabolite hydroxyBPR,^{295,296} and some of them include more than one metabolite, usually erythrohydroBPR and threoBPR.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/MS³⁰⁵ 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

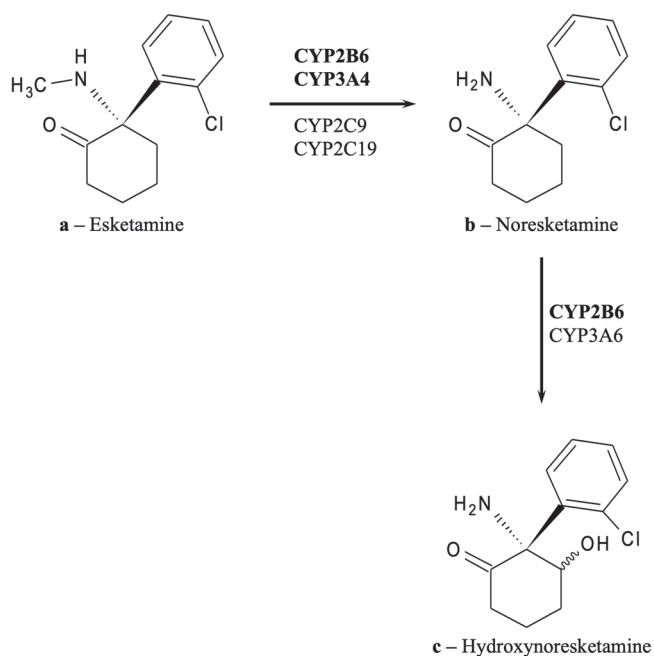
8.1 | Esketamine

Esketamine ((2S)-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 activity³¹⁴ 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 enhancement³²³ 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

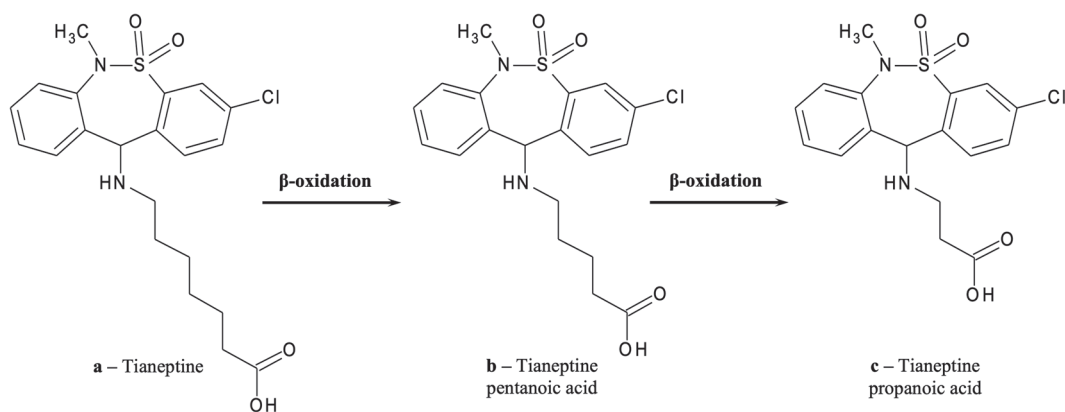


FIGURE 12 Main metabolic pathway of tianeptine. CYP, cytochrome P 450

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 trough (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 metabolite³³²; another one carries out the determination of TNP alone.³³³ Other methods include HPLC-FL after derivatization³³⁴ 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, Boehringer, 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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REFERENCES

1. Morin RT, Nelson C, Bickford D, Insel PS, Mackin RS. Somatic and anxiety symptoms of depression are associated with disability in late life depression. *Aging Ment Health*. 2019;4:1-4.
2. Gahr M, Uzelac Z, Zeiss R, Connemann BJ, Lang D, Schönfeldt-Lecuona C. Linking annual prescription volume of antidepressants to corresponding web search query data: a possible proxy for medical prescription behavior? *J Clin Psychopharmacol*. 2015;35:681-685.
3. Rathod S, Pinninti N, Irfan M, et al. Mental health service provision in low- and middle-income countries. *Health Serv Insights*. 2017;10:1178632917694350.
4. Furukawa TA, Salanti G, Atkinson LZ, et al. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. *BMJ Open*. 2016;6:e010919.
5. Luo Y, Chaimani A, Kataoka Y, et al. Evidence synthesis, practice guidelines and real-world prescriptions of new generation antidepressants in the treatment of depression: a protocol for cumulative network meta-analyses and meta-epidemiological study. *BMJ Open*. 2018;8:e023222.
6. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51:215-235.
7. Malberg JE, Blendy JA. Antidepressant action: to the nucleus and beyond. *Trends Pharmacol Sci*. 2005;26:631-638.
8. Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues Clin Neurosci*. 2008;10:385-400.
9. Tylee A, Walters P. Onset of action of antidepressants. *BMJ*. 2007;334:911-912.
10. Li Y-F. Strategy for development of fast-onset antidepressive agents: candidate hypothesis of monoamine (5-HT)-nonmonoamine (Glu/GABA) long-feedback neural circuit. *Chinese J Pharmacol Toxicol*. 2019;33:161-173.
11. Garay RP, Zarate CA Jr, Charpeaud T, et al. Investigational drugs in recent clinical trials for treatment-resistant depression. *Expert Rev Neurother*. 2017;17:593-609.
12. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: the way toward the personalization of antidepressant treatment. *Can J Psychiat*. 2014;59:62-75.
13. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence economic outcomes. *Med Care*. 2006;44:300-303.
14. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. *J Clin Psychiat*. 2003;64:18-25.
15. Fabbri C, Kasper S, Kautzky A, et al. A polygenic predictor of treatment-resistant depression using whole exome sequencing and genome-wide genotyping. <https://www.medrxiv.org/content/10.1101/19007161v1> Accessed October 10, 2019.
16. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol*. 2001;52:45-54.
17. Raggi MA, Mandrioli R, Sabbioni C, Pucci V. Atypical antipsychotics: pharmacokinetics, therapeutic drug monitoring and pharmacological interactions. *Curr Med Chem*. 2004;11:279-296.
18. Albers LJ, Ozdemir V. Pharmacogenomic-guided rational therapeutic drug monitoring: conceptual framework and application platforms for atypical antipsychotics. *Curr Med Chem*. 2004;11:297-312.
19. Bauer M, Severus E, Köhler S, Whybrow PC, Angst J, Möller HJ. WFSBP task force on treatment guidelines for unipolar depressive disorders. World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder-update 2015. *World J Biol Psychiat*. 2015;12:76-95.
20. Conca A, Schmidt E, Pastore M, Hiemke C, Duffy D, Giupponi G. Therapeutic drug monitoring in Italian psychiatry. *Pharmacopsychiatry*. 2011;44:259-262.
21. Wong SHY, Sunshine I. *Handbook of Analytical Therapeutic Drug Monitoring and Toxicology*. Boca Raton, FL: CRC Press; 1997:368.
22. Raggi MA, Mandrioli R, Pucci V, Sabbioni C. Advances in therapeutic drug monitoring of atypical antipsychotic drugs. *Med Chem Rev Online*. 2004;1:299-316.
23. Mandrioli R, Protti M, Mercolini L. Novel atypical antipsychotics: metabolism and therapeutic drug monitoring (TDM). *Curr Drug Metab*. 2014;16:141-151.
24. Mandrioli R, Protti M, Mercolini L. Metabolic syndrome in schizophrenia: focus on the role of antipsychotic medications and indications for therapeutic drug monitoring (TDM) methods. In: *Frontiers in Clinical Drug Research – Diabetes and Obesity Vol. 5*. Sharjah: Bentham Science Publishers; 2020. In press. DOI: 10.2174/97816810875351190501

25. Mercolini L, Protti M, Fulgenzi G, et al. A fast and feasible microextraction by packed sorbent (MEPS) procedure for HPLC analysis of the atypical antipsychotic ziprasidone in human plasma. *J Pharmaceut Biomed*. 2014;88:467-471.
26. Mandrioli R, Mercolini L, Raggi MA. Benzodiazepine metabolism: an analytical perspective. *Curr Drug Metab*. 2008;9:827-844.
27. Mandrioli R, Mercolini L, Raggi MA. Metabolism of benzodiazepine and non-benzodiazepine anxiolytic-hypnotic drugs: an analytical point of view. *Curr Drug Metab*. 2010;11:815-829.
28. Mandrioli R, Mercolini L. Metabolism of drugs used in the therapy of seizures: an analytical point of view. Part 1. *Curr Drug Metab*. 2017;18(8):735-756.
29. Capuano B, Crosby IT, Lloyd EJ. Schizophrenia: genesis, receptorology and current therapeutics. *Curr Med Chem*. 2002;9:521-548.
30. Mandrioli R, Mercolini L, Saracino MA, Raggi MA. Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. *Curr Med Chem*. 2012;19:1846-1863.
31. Wille SMR, Cooreman SG, Neels HM, Lambert WEE. Relevant issues in the monitoring and the toxicology of antidepressants. *Crit Rev Clin Lab Sci*. 2008;45:25-89.
32. Baumann P, Hiemke C, Ulrich S, et al. Arbeitsgemeinschaft für neuropsychopharmakologie und pharmakopsychiatrie. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry*. 2004;37:243-265.
33. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:9-62.
34. Mandrioli R, Protti M, Mercolini L. New-generation, non-SSRI antidepressants: therapeutic drug monitoring and pharmacological interactions. Part 1: SNRIs, SMSs, SARIs. *Curr Med Chem*. 2018;25:772-792.
35. Elsevier BV, Scopus document search 2019. <https://www.scopus.com/home.uri>. Accessed September 10, 2019.
36. National Center for Biotechnology Information. PubMed Search 2019. <https://www.ncbi.nlm.nih.gov/pubmed>. Accessed September 10, 2019.
37. Medicines.org.au, Tolvon product information. <http://www.medicines.org.au/files/mkptolvo.pdf>. Accessed September 10, 2019.
38. Olumuyiwa JF. The emergence of new antidepressants for clinical use: Agomelatine paradox versus other novel agents. *IBRO Reports*. 2019;6:95-110.
39. Ban TA, ed. (Ed.). *An oral history of neuropsychopharmacology. The first fifty years. Vol. 9: Update*. Brentwood: American College of Neuropsychopharmacology; 2011.
40. Drugbank. Drug interaction lookup. https://www.drugbank.ca/interax/drug_lookup. Accessed September 10, 2019.
41. Demling J. Mianserin: pharmacology and clinical aspects of an effective antidepressive agent. *Fortschr Med*. 1993;111:497-500.
42. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. *J Pharmacol Exp Ther*. 1984;230:94-102.
43. Olanas MC, Dedoni S, Onali P. The atypical antidepressant mianserin exhibits agonist activity at κ -opioid receptors. *Br J Pharmacol*. 2012;167:1329-1341.
44. Herman I, Shamir D, Bar-Hamburger R, Pick CG, Schreiber S. The effect of mianserin add-on, on the intensity of opioid withdrawal symptoms during detoxification program - a randomized, double blind, placebo controlled, prospective study. *Addictive Behav*. 2005;30:1154-1167.
45. Pinder RM, van Delft AM. Pharmacological aspects of mianserin. *Acta Psychiatr Scand Suppl*. 1983;302:59-71.
46. Koyama E, Chiba K, Tani M, Ishizaki T. Identification of human cytochrome P450 isoforms involved in the stereoselective metabolism of mianserin enantiomers. *J Pharmacol Exp Ther*. 1996;278:21-30.
47. Chow T, Hiroi T, Imaoka S, Chiba K, Funae Y. Isoform-selective metabolism of mianserin by cytochrome P-450 2D. *Drug Metab Dispos*. 1999;27:1200-1204.
48. Otani K, Sasa H, Kaneko S, Kondo T, Fukushima Y. Steady-state plasma concentrations of mianserin and its major active metabolite, desmethylmianserin. *Ther Drug Monit*. 1993;15:113-117.
49. Poleszak E, Szopa A, Wyska E, et al. Caffeine augments the antidepressant-like activity of mianserin and agomelatine in forced swim and tail suspension tests in mice. *Pharmacol Rep*. 2016;68:56-61.
50. Socała K, Nieoczym D, Wyska E, Poleszak E, Wlaż P. Sildenafil, a phosphodiesterase type 5 inhibitor, enhances the activity of two atypical antidepressant drugs, mianserin and tianeptine, in the forced swim test in mice. *Prog Neuro-Psychoph*. 2012;38:121-126.
51. Stasiuk W, Serefko A, Szopa A, et al. Traxoprodil augments the antidepressant-like activity of agomelatine but not of mianserin or tianeptine in the forced swim test in mice. *Pharmacol Rep*. 2016;68:960-963.
52. Górska D, Andrzejczak D. Influence of mianserin on the activity of some hypotensive drugs in spontaneously hypertensive rats. *Polish J Pharmacol*. 2003;55:409-417.

53. Pakulska W, Czarnecka E. Influence of mianserin on the antinociceptive effect of morphine, metamizol and indomethacin in mice. *Pharmacol Res.* 2002;46:415-423.
54. Montgomery S, McAuley R, Montgomery DB. Relationship between mianserin plasma levels and antidepressant effect in a double-blind trial comparing a single night-time and divided daily dose regimens. *Br J Clin Pharmacol.* 1978; 5(Suppl 1):71S-76S.
55. Xu P, Li H-D, Chen B-M, Ma N, Yan M, Zhu Y-G. Determination of mianserin in human plasma by high performance liquid chromatography-electrospray ionization mass spectrometry (HPLC-ESI/MS): application to a bioequivalence study in Chinese volunteers. *J Pharmaceut Biomed.* 2008;47:994-999.
56. Chauhan B, Rani S, Guttikar S, Zope A, Jadon N, Padh H. Analytical method development and validation of mianserin hydrochloride and its metabolite in human plasma by LC-MS. *J Chromatogr B.* 2005;823:69-74.
57. Hefnawy MM, Aboul-Enein HY. Fast high-performance liquid chromatographic analysis of mianserin and its metabolites in human plasma using monolithic silica column and solid phase extraction. *Anal Chim Acta.* 2004;504:291-297.
58. Łukaszkiewicz J, Piwowarska J, Skarzyńska E, Łojewska MS, Pachecka J. Development, validation and application of the HPLC method for determination of mianserin in human serum. *Acta Pol Pharm - Drug Res.* 2007;64:103-107.
59. Grodner B, Pachecka J. A simpler and faster capillary electrophoresis method for determination of mianserin enantiomers in human serum. *Acta Pol Pharm- Drug Res.* 2006;63:9-14.
60. Ishii A, Kurihara R, Kojima T, et al. Sensitive determination of mianserin and setiptiline in body fluids by gas chromatography with surface ionizations detection (GC-SID). *Legal Med.* 2000;2:115-118.
61. Li W, Wu D, Chen S, Peng H, Guan Y. Study of the surface ionization detector for gas chromatography. *J Chromatogr A.* 2011;1218:6812-6816.
62. Food and Drug Administration, Mirtazapine Approval History. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#aphhist. Accessed September 10, 2019.
63. Liappas J, Paparrigopoulos T, Tzavellas E, Christodoulou G. Alcohol detoxification and social anxiety symptoms: a preliminary study of the impact of mirtazapine administration. *J Affect Disord.* 2003;76:279-284.
64. Poyurovsky M, Epshtein S, Fuchs C, Schneidman M, Weizman R, Weizman A. Efficacy of low-dose mirtazapine in neuroleptic-induced akathisia: a double-blind randomized placebo-controlled pilot study. *J Clin Psychopharmacol.* 2003;23:305-308.
65. Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev.* 2001;7: 249-264.
66. Wan DD, Kundhur D, Solomons K, Yatham LN, Lam RW. Mirtazapine for treatment-resistant depression: a preliminary report. *J Psychiatry Neurosci.* 2003;28:55-59.
67. Van Hensbeek I, Van Oers H, Schutte AJ. Early onset of action of mirtazapine versus other new-generation antidepressants for patients in remission. *Eur Neuropsychopharm.* 2002;12:187. -187.
68. Raggi MA, Mandrioli R, Pucci V. New trends in the treatment of depression: pharmacological profiles of selective serotonin reuptake inhibitors. *Curr Trends Med Chem.* 2003;3:203-220.
69. Wheatley DP, van Moffaert M, Timmerman L, Kremer CM. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psychiat.* 1998;59:306-312.
70. Störmer E, von Moltke LL, Shader RI, Greenblatt DJ. Metabolism of the antidepressant mirtazapine in vitro: contribution of cytochromes P-450 1A2, 2D6, and 3A4. *Drug Metab Dispos.* 2000;28:1168-1175.
71. Dodd S, Boulton DW, Burrows GD, De Vane CL, Norman TR. In vitro metabolism of mirtazapine enantiomers by human cytochrome P450 enzymes. *Hum Psychopharmacol.* 2001;16:541-544.
72. Delbressine LP, Moonen ME, Kaspersen FM, et al. Pharmacokinetics and biotransformation of mirtazapine in human volunteers. *Clin Drug Investig.* 1998;15:45-55.
73. Delbressine LP, Vos RM. The clinical relevance of preclinical data: mirtazapine, a model compound. *J Clin Psychopharmacol.* 1997;17S1:29S-33S.
74. Dahl M-L, Voortman G, Alm C, et al. In vitro and in vivo studies on the disposition of mirtazapine in humans. *Clin Drug Invest.* 1997;13:37-46.
75. Moody JD, Freeman JP, Fu PP, Cerniglia CE. Biotransformation of mirtazapine by *Cunninghamella elegans*. *Drug Metab Dispos.* 2002;30:1274-1279.
76. Holzbach R, Jahn H, Pajonk FG, Mähne C. Suicide attempts with mirtazapine overdose without complications. *Biol Psychiat.* 1998;44:925-926.
77. Nutt DJ. Tolerability and safety aspects of mirtazapine. *Hum Psychopharmacol.* 2002;17S1:S37-S41.
78. Sweetman SC, ed. *Martindale The Complete Drug Reference.* 34 ed. London, UK: Pharmaceutical Press; 2004:299.
79. Health Canada, Health Canada advises Canadians of stronger warnings for SSRIs and other newer anti-depressants. <https://www.canada.ca/en/news/archive/2004/06/health-canada-advises-canadians-stronger-warnings-ssris-other-newer-anti-depressants.html>. Accessed September 10, 2019.
80. Devi S. Antidepressant-suicide link in children questioned. *Lancet.* 2012;379:791.

81. Loonen AJ, Doorschot CH, Oostelbos MC, Sitsen JM. Lack of drug interactions between mirtazapine and risperidone in psychiatric patients: a pilot study. *Eur Neuropsychopharmacol.* 1999;10:51-57.
82. Zoccali R, Muscatello MR, Torre DL, et al. Lack of a pharmacokinetic interaction between mirtazapine and the newer antipsychotics clozapine, risperidone and olanzapine in patients with chronic schizophrenia. *Pharmacol Res.* 2003;48:411-414.
83. Paulzen M, Haen E, Hiemke C, et al. Antidepressant polypharmacy and the potential of pharmacokinetic interactions: doxepin but not mirtazapine causes clinically relevant changes in venlafaxine metabolism. *J Affect Disorders.* 2017;227:506-511.
84. Lo Presti C, Laguin S, Bambina E, Arlotto E, Aghazarian V, Guise-Honore S. Case report: pharmacokinetic interaction between clozapine and mirtazapine. *Encephale.* 2019;45(4):363-364.
85. Ginsberg DL. Mirtazapine-risperidone combination associated with pulmonary thromboembolism and rhabdomyolysis. *Prim Psychiat.* 2006;13:25-26.
86. Abbasi SH, Behpournia H, Ghoreishi A, et al. The effect of mirtazapine add on therapy to risperidone in the treatment of schizophrenia: a double-blind randomized placebo-controlled trial. *Schizophr Res.* 2010;116:101-106.
87. Cho SJ, Yook K, Kim B, et al. Mirtazapine augmentation enhances cognitive and reduces negative symptoms in schizophrenia patients treated with risperidone: a randomized controlled trial. *Prog Neuro-Psychoph.* 2011;35:208-211.
88. Stenberg J-H, Terevnikov V, Joffe M, et al. More evidence on proneurocognitive effects of add-on mirtazapine in schizophrenia. *Prog Neuro-Psychoph.* 2011;35:1080-1086.
89. Terevnikov V, Stenberg JH, Tiihonen J, et al. Add-on mirtazapine improves depressive symptoms in schizophrenia: a double-blind placebo-controlled study with an open label extension phase. *Hum Psychopharmacol.* 2011;26:188-193.
90. Berk M, Gama CS, Sundram S, et al. Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: a double-blind, randomised, placebo-controlled clinical trial. *Hum Psychopharmacol.* 2009;24:233-238.
91. Rogóz Z. Effect of combined treatment with mirtazapine and risperidone on the MK-801-induced changes in the object recognition test in mice. *Pharmacol Rep.* 2013;65:1401-1406.
92. Page RL 2nd, Ruscin JM, Bainbridge JL, Brieke AA. Restless legs syndrome induced by escitalopram: case report and review of the literature. *Pharmacotherapy.* 2008;28:271-280.
93. Prospero-Garcia KA, Torres-Ruiz A, Ramirez-Bermudez J, Yelazquez-Moctezuma J, Arana-Lechuga Y, Teran-Perez G. Fluoxetine-mirtazapine interaction may induce restless legs syndrome: report of 3 cases from a clinical trial. *J Clin Psychiat.* 2006;67:1820.
94. Orlandi V, Specia A, Salviati M, Biondi M. Abnormal prolactin elevation in a schizophrenic patient in treatment with quetiapine and mirtazapine. The role of the opioid system. *J Clin Psychopharmacol.* 2003;23:677-679.
95. Nishimura H, Kawakami M. A case with the increased PT-INR after the addition of mirtazapine to warfarin therapy. *Psychiat Neurol Japon.* 2015;117:820-825.
96. Rajpurohit N, Aryal SR, Khan MA, Stys AT, Stys TP. Propafenone-associated severe central nervous system and cardiovascular toxicity due to mirtazapine: a case of severe drug interaction. *South Dakota Med.* 2014;67:137-139.
97. Koch H, Nanev D. Important interaction between mirtazapine and ondansetron. *Afr J Psychiatry.* 2012;15:160. -160.
98. Lozano R. Mirtazapine and ondansetron: a dual pharmacodynamic and pharmacokinetic interaction. *Afr J Psychiatry.* 2013;16:56.
99. Fraile P, Garcia-Cosmes P, Garcia T, Corbacho L, Alvarez M, Taberner JM. Hypotension, as consequence of the interaction between tacrolimus and mirtazapine, in a patient with renal transplant. *Nephrol Dial Transpl.* 2009;24:1999-2001.
100. Barbosa-Méndez S, Matus-Ortega M, Salazar-Juárez A. Synergistic interactions between mirtazapine and prazosin prevent the induction and expression of behavioral sensitization to cocaine in rats. *Physiol Behav.* 2017;180:137-145.
101. Andrzejczak D, Kocon K, Zięba R. Influence of mirtazapine on the hypotensive activity of enalapril and propranolol in spontaneously hypertensive rats. *Basic Clin Pharmacol.* 2008;103:450-454.
102. Thakar BN, Shah K, Desai U, Suresh DK, Rawal R, Khalid S. Modulation in pharmacokinetic properties of mirtazapine and citalopram during contemporaneous therapy with ritonavir. *J Pharmacol Toxicol.* 2012;7:29-37.
103. Grasmader K, Verwohlt PL, Kuhn KU, et al. Relationship between mirtazapine dose, plasma concentration, response, and side effects in clinical practice. *Pharmacopsychiatry.* 2005;38:113-117.
104. Ptáček P, Klíma J, Macek J. Determination of mirtazapine in human plasma by liquid chromatography. *J Chromatogr B.* 2003;794:323-328.
105. Dodd S, Burrows GD, Norman TR. Chiral determination of mirtazapine in human blood plasma by high-performance liquid chromatography. *J Chromatogr B.* 2000;748:439-443.
106. Paus E, Jonzier-Perey M, Cochard N, Eap CB, Baumann P. Chirality in the new generation of antidepressants: stereoselective analysis of the enantiomers of mirtazapine, N-demethylmirtazapine, and 8-hydroxymirtazapine by LC-MS. *Ther Drug Monit.* 2004;26:366-374.

107. Pistos C, Koutsopoulou M, Panderi I. Validated liquid chromatography-tandem mass spectrometry method for the determination of mirtazapine and demethylmirtazapine in human plasma: application to a pharmacokinetic study. *Anal Chim Acta*. 2004;514:15-26.
108. Romiguières T, Pehourcq F, Matoga M, Begaud B, Jarry C. Determination of mirtazapine and its demethyl metabolite in plasma by high-performance liquid chromatography with ultraviolet detection. Application to management of acute intoxication. *J Chromatogr B*. 2002;775:163-168.
109. Maris FA, Dingler E, Niehues S. High-performance liquid chromatographic assay with fluorescence detection for the routine monitoring of the antidepressant mirtazapine and its demethyl metabolite in human plasma. *J Chromatogr B*. 1999;721:309-316.
110. Mandrioli R, Mercolini L, Ghedini N, Bartoletti C, Fanali S, Raggi MA. Determination of the recent antidepressant mirtazapine and its two main metabolites in human plasma by liquid chromatography with fluorescence detection. *Anal Chim Acta*. 2006;556:281-288.
111. Meineke I, Kress I, Poser W, Rütther E, Brockmöller J. Therapeutic drug monitoring of mirtazapine and its metabolite desmethylmirtazapine by HPLC with fluorescence detection. *Ther Drug Monit*. 2004;26:277-283.
112. Shams M, Hiemke C, Härtter S. Therapeutic drug monitoring of the antidepressant mirtazapine and its N-demethylated metabolite in human serum. *Ther Drug Monit*. 2004;26:78-84.
113. Morgan PE, Tapper J, Spencer EP. Measurement of total mirtazapine and normirtazapine in plasma/serum by liquid chromatography with fluorescence detection. *J Chromatogr B*. 2003;798:211-215.
114. de Santana FJ, Cesarino EJ, Bonato PS. New method for the chiral evaluation of mirtazapine in human plasma by liquid chromatography. *J Chromatogr B*. 2004;809:351-356.
115. Mandrioli R, Pucci V, Sabbioni C, Bartoletti C, Fanali S, Raggi MA. Enantioselective determination of the novel antidepressant mirtazapine and its active demethylated metabolite in human plasma by means of capillary electrophoresis. *J Chromatogr A*. 2004;1051:253-260.
116. Fanali S, Aturki Z, Kasicka V, Raggi MA, D'Orazio G. Enantiomeric separation of mirtazapine and its metabolites by nano-liquid chromatography with UV-absorption and mass spectrometric detection. *J Sep Sci*. 2005;28:1719-1728.
117. Mandrioli R, Raggi MA. Advances in the enantioseparation of second-generation antidepressant drugs by electrodriven methods. *Electrophoresis*. 2006;27:213-221.
118. Niho T, Ito C, Shibutani Y, Hashizume H, Yamaguchi K. Pharmacological properties of MO-8282: a novel antidepressant. *Jpn J Pharmacol*. 1986;88:309-320.
119. Mizota M, Oikawa Y, Nakayama K, et al. Pharmacological studies of MO-8282: a new antidepressant. *Jpn J Pharmacol*. 1986;88:457-466.
120. Przegaliński E, Baran L, Siwanowicz J, Rawłów A. The lack of antidepressant properties and a potent central antiserotonin activity of Org 8282. *Pol J Pharmacol Pharm*. 1986;38:377-384.
121. Matsumoto S. Effect of setiptiline maleate, an antidepressant, on the activities of human liver cytochrome P450 - comparison with fluvoxamine maleate. *Jpn Pharmacol Ther*. 2001;29:45-50.
122. Makoto K, Anri A, Noboru Y, et al. The effect of age on plasma level of setiptiline maleate in depressed patients. *Prog Neuro-Psychoph*. 1994;18:1015-1026.
123. Brenner E, Baldwin RM, Tamagnan G. Asymmetric synthesis of (+)-(S,S)- Reboxetine via a new (S)-2-2(Hydroxymethyl) morpholine preparation. *Org Lett*. 2005;7:937-939.
124. Page ME. The promises and pitfalls of reboxetine. *CNS Drug Rev*. 2003;9:327-342.
125. Hajos M, Fleishaker JC, Filipiak-Reisner JK, Brown MT, Wong EHF. The selective norepinephrine reuptake inhibitor antidepressant reboxetine: pharmacological and clinical profile. *CNS Drug Rev*. 2004;10:23-44.
126. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokin*. 2000;39:413-427.
127. De Vane CL, Boulton DW. Great expectations in stereochemistry: Focus on antidepressants. *CNS Spectr*. 2002;7:28-33.
128. Fleishaker JC, Mucci M, Pellizzoni C, Poggesi I. Absolute bioavailability of reboxetine enantiomers and effect of gender on pharmacokinetics. *Biopharm Drug Dispos*. 1999;20:53-57.
129. Wienkers LC, Allievi C, Hauer MJ, Wynalda MA. Cytochrome P450-mediated metabolism of the individual enantiomers of the antidepressant agent reboxetine in human liver microsomes. *Drug Metab Dispos*. 1995;27:1334-1340.
130. Hysek CM, Simmler LD, Ineichen M, et al. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (ecstasy) in humans. *Clin Pharm Ther*. 2011;90:246-255.
131. Schüle C, Baghai T, Laakmann G. Mirtazapine decreases stimulatory effects of reboxetine on cortisol, adrenocorticotropin and prolactin secretion in healthy male subjects. *Neuroendocrinology*. 2004;79:54-62.
132. Kuhn UD, Kirsch M, Merkel U, et al. Reboxetine and cytochrome P450 - comparison with paroxetine treatment in humans. *Int J Clin Pharm Ther*. 2007;45:36-46.

133. Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Levita A. No effect of reboxetine on plasma concentrations of clozapine, risperidone, and their active metabolites. *Ther Drug Monit.* 2001;23:675-678.
134. Serretti A, Lucca A, Cusin C, Smeraldi E. Effect of reboxetine augmentation in SSRI resistant patients. *Giorn Ital Psicopat.* 2001;7:9-14.
135. Poptawska M, Wróblewska D, Borowicz KK. Interactions between an antidepressant reboxetine and four classic antiepileptic drugs in the mouse model of myoclonic seizures. *Pharmacol Rep.* 2015;67:1141-1146.
136. Borowicz KK, Zarczuk R, Latalski M, Borowicz KM. Reboxetine and its influence on the action of classical antiepileptic drugs in the mouse maximal electroshock model. *Pharmacol Rep.* 2014;66:430-435.
137. Öhman D, Norlander B, Peterson C, Bengtsson F. Bioanalysis of racemic reboxetine and its desethylated metabolite in a therapeutic drug monitoring setting using solid phase extraction and HPLC. *Ther Drug Monit.* 2001;23:27-34.
138. Frigerio E, Pianezzola E, Strolin Benedetti M. Sensitive procedure for the determination of reboxetine enantiomers in human plasma by reversed-phase high-performance liquid chromatography with fluorimetric detection after chiral derivatization with (+)-1-(9-fluorenyl)ethyl chloroformate. *J Chromatogr A.* 1994;660:351-358.
139. Walters RR, Buist SC. Improved enantioselective method for the determination of the enantiomers of reboxetine in plasma by solid-phase extraction, chiral derivatization, and column-switching high-performance liquid chromatography with fluorescence detection. *J Chromatogr A.* 1998;828:167-176.
140. Khalil NY. A highly sensitive HPLC method with automated on-line sample pre-treatment and fluorescence detection for determination of reboxetine in human plasma. *Talanta.* 2010;80:1251-1256.
141. Härtter S, Weigmann H, Hiemke C. Automated determination of reboxetine by high-performance liquid chromatography with column-switching and ultraviolet detection. *J Chromatogr B.* 2000;740:135-140.
142. Edwards DM, Pellizzoni C, Breuel HP, et al. Pharmacokinetics of reboxetine in healthy volunteers. Single oral doses, linearity and plasma protein binding. *Biopharm Drug Dispos.* 1995;16:443-460.
143. Öhman D, Norlander B, Peterson C, Bengtsson F. Simultaneous determination of reboxetine and O-desethylreboxetine enantiomers using enantioselective reversed-phase high-performance liquid chromatography. *J Chromatogr A.* 2002;947:247-254.
144. Déglon J, Lauer E, Thomas A, Mangin P, Staub C. Use of the dried blood spot sampling process coupled with fast gas chromatography and negative-ion chemical ionization tandem mass spectrometry: application to fluoxetine, norfluoxetine, reboxetine, and paroxetine analysis. *Anal Bioanal Chem.* 2010;396:2523-2532.
145. Fleishaker JC, Francom SF, Herman BD, Knuth DW, Azie NE. Lack of effect of reboxetine on cardiac repolarization. *Clin Pharmacol Ther.* 2001;70:261-269.
146. Öhman D, Cherma MD, Norlander B, Bengtsson F. Determination of serum reboxetine enantiomers in patients on chronic medication with racemic reboxetine. *Ther Drug Monit.* 2003;25:174-182.
147. Zoerner AA, Schroeder C, Kayacelebi AA, et al. A validated, rapid UPLC-MS/MS method for simultaneous ivabradine, reboxetine, and metoprolol analysis in human plasma and its application to clinical trial samples. *J Chromatogr B.* 2013; 927:105-111.
148. Raggi MA, Mandrioli R, Sabbioni C, Parenti C, Cannazza G, Fanali S. Separation of reboxetine enantiomers by means of capillary electrophoresis. *Electrophoresis.* 2002;23:1870-1877.
149. Ficarra R, Calabrò ML, Tommasini S, Melardi S, Cutroneo P, Ficarra P. Direct separation of the enantiomers of reboxetine by liquid chromatography on different cellulose- and amylose-based chiral stationary phases. *Chromatographia.* 2001;53:261-265.
150. Cannazza G, Braghiroli D, Carrozzo MM, et al. Enantioseparation of the antidepressant reboxetine. *J Pharmaceut Biomed.* 2008;48(3):991-996.
151. Lemke TL, Williams DA, eds. (Eds.). *Foye's Principles of Medicinal Chemistry 6th Edition* Baltimore and Philadelphia; Lippincott Williams & Wilkins: 2008.
152. Roers E, Adewole T, Johnson JK, Brittain ST. Single and multiple ascending dose study to evaluate the safety, tolerability, and cardiac safety of extended-release viloxazine (SPN-812 ER) in healthy adult subjects. <http://www.psychiatrist.com/ascpabstracts/documents/ascpabstracts.pdf>. Accessed September 15, 2019.
153. Blackburn TP, Foster GA, Greenwood DT, Howe R. Effects of viloxazine, its optical isomers and its major metabolites on biogenic amine uptake mechanisms in vitro and in vivo. *Eur J Pharmacol.* 1978;52:367-374.
154. Danchev ND, Rozhanets VV, Zhmurenko LA, Glozman OM, Zagorevskii VA. Behavioral and radioreceptor analysis of viloxazine stereoisomers. *Bull Exp Biol Med.* 1984;97:576-578.
155. Case DE, Reeves PR. The disposition and metabolism of ECI 58,834 (viloxazine) in humans. *Xenobiotica.* 1975;5: 113-129.
156. Badolo L, Jensen B, Säll C, Norinder U, Kallunki P, Montanari D. Evaluation of 309 molecules as inducers of CYP3A4:CYP2B6:CYP1A2:OATP1B1:OCT1:MDR1:MRP2:MRP3 and BCRP in cryopreserved human hepatocytes in sandwich culture. *Xenobiotica.* 2015;45:177-187.

157. Wang B, Zhou SF. Synthetic and natural compounds that interact with human cytochrome P450 1A2 and implications in drug development. *Curr Med Chem*. 2009;16:4066-4218.
158. Pisani F, Narbone MC, Fazio A, et al. Effect of viloxazine on serum carbamazepine levels in epileptic patients. *Epilepsia*. 1984;25:482-485.
159. Pisani F, Fazio A, Artesi C, et al. Elevation of plasma phenytoin by viloxazine in epileptic patients: a clinically significant drug interaction. *J Neurol Neurosurg Psychiatry*. 1992;55:126-127.
160. Pisani F, Fazio A, Oteri G, et al. Effects of the antidepressant drug viloxazine on oxcarbazepine and its hydroxylated metabolites in patients with epilepsy. *Acta Neurol Scand*. 1994;90:130-132.
161. Odou P, Geronimi-Ferret D, Degen P, Robert H. Viloxazine-carbamazepine. Dangerous double-interaction? One case study. *J Pharm Clin*. 1996;15:157-160.
162. Pleece SA, Kirby MJ, Redfern PH. The effect of viloxazine on drug-induced inhibition of food intake in the rat. *J Pharm Pharmacol*. 1980;32:558-560.
163. Norman TR, Burrows GD, Davies BM, Maguire KP, Wurm JM. Viloxazine plasma concentrations and clinical response. *J Affect Disord*. 1980;2:157-164.
164. Falcy M, Riboulet-Delmas G, Efthymiou ML. Acute poisoning by viloxazine chlorhydrate taken by itself. *Encephale*. 1983;9:137-144.
165. Jourdil NH, Fontanille PD, Bessard GM. Concurrent determination of second-generation anti-depressants in plasma by using gas chromatography with nitrogen-phosphorus detection. *Clin Chem*. 1997;43:2209-2210.
166. Martínez MA, Sánchez de la Torre C, Almarza E. Simultaneous determination of viloxazine, venlafaxine, imipramine, desipramine, sertraline, and amoxapine in whole blood: comparison of two extraction/cleanup procedures for capillary gas chromatography with nitrogen-phosphorus detection. *J Anal Toxicol*. 2002;26:296-302.
167. Fazio A, Crisafulli P, Primerano G, D'Agostino AA, Oteri G, Pisani F. A sensitive gas chromatographic assay for the determination of serum viloxazine concentration using a nitrogen-phosphorus-selective detector. *Ther Drug Monit*. 1984;6:484-488.
168. Wille SMR, De Letter EA, Piette MHA, Van Overschelde LK, Van Peteghem CH, Lambert WE. Determination of antidepressants in human postmortem blood, brain tissue, and hair using gas chromatography-mass spectrometry. *Int J Legal Med*. 2009;123:451-458.
169. Wille SMR, Van Hee P, Neels HM, Van Peteghem CH, Lambert WE. Comparison of electron and chemical ionization modes by validation of a quantitative gas chromatographic-mass spectrometric assay of new generation anti-depressants and their active metabolites in plasma. *J Chromatogr A*. 2007;1176:236-245.
170. Titier K, Castaing N, Le-Déodic M, Le-Bars D, Moore N, Molimard M. Quantification of tricyclic antidepressants and monoamine oxidase inhibitors by high-performance liquid chromatography-tandem mass spectrometry in whole blood. *J Anal Toxicol*. 2007;31:200-207.
171. Duverneuil C, De la Grandmaison GL, De Mazancourt P, Alvarez JC. A high-performance liquid chromatography method with photodiode-array UV detection for therapeutic drug monitoring of the nontricyclic antidepressant drugs. *Ther Drug Monit*. 2003;25:565-573.
172. Tracqui A, Kintz P, Kreissig P, Mangin P. A simple and rapid method for toxicological screening of 25 antidepressants in blood or urine using high performance liquid chromatography with diode-array detection. *Ann Biol Clin*. 1992;50:639-647.
173. Garrido EMPJ, Garrido JMPJ, Esteves M, Santos-Silva A, Marques MPM, Borges F. Voltammetric and DFT studies on viloxazine: analytical application to pharmaceuticals and biological fluids. *Electroanalysis*. 2008;20:1454-1462.
174. Ogura C, Kishimoto A, Kunimoto N, et al. Clinical pharmacology of a new antidepressant, Y-8894 in healthy young and elderly volunteers. *Br J Clin Pharmacol*. 1987;23:537-543.
175. Saka C. Analytical strategies for the determination of norepinephrine reuptake inhibitors in pharmaceutical formulations and biological fluids. *Crit Rev Anal Chem*. 2016;46:40-66.
176. Orlando R, Benvenuti C, Mazzo M, Palatini P. The pharmacokinetics of teniloxazine in healthy subjects and patients with hepatic cirrhosis. *Br J Clin Pharmacol*. 1995;39:445-448.
177. American Society of Health-System Pharmacists. Atomoxetine hydrochloride. <https://www.drugs.com/monograph/atomoxetine-hydrochloride.html>. Accessed September 15, 2019.
178. Huang KL, Wei HT, Hsu JW, et al. Risk of suicide attempts in adolescents and young adults with attention-deficit hyperactivity disorder: a nationwide longitudinal study. *Br J Psychiat*. 2018;212:234-238.
179. Kim S-H, Byeon J-Y, Kim Y-H, et al. Physiologically based pharmacokinetic modelling of atomoxetine with regard to CYP2D6 genotypes. *Sci Rep*. 2018;8:8.
180. Sauer JM, Ponsler GD, Mattiuzi EL, et al. Disposition and metabolic fate of atomoxetine hydrochloride: the role of CYP2D6 in human disposition and metabolism. *Drug Metab Dispos*. 2003;31:98-107.
181. Sauer JM, Ring BJ, Witcher JW. Clinical pharmacokinetics of atomoxetine. *Clin Pharmacokin*. 2005;44:571-590.

182. Ring BJ, Gillespie JS, Eckstein JA, Wrighton SA. Identification of the human cytochromes P450 responsible for atomoxetine metabolism. *Drug Metab Dispos.* 2002;30:319-323.
183. Dinh JC, Pearce RE, Van Haandel L, Gaedigk A, Leeder JS. Characterization of atomoxetine biotransformation and implications for development of PBPK models for dose individualization in children. *Drug Metab Dispos.* 2016;44:1070-1079.
184. Todor I, Popa A, Neag M, et al. Evaluation of the potential pharmacokinetic interaction between atomoxetine and fluvoxamine in healthy volunteers. *Pharmacology.* 2017;99:84-88.
185. Todor I, Popa A, Neag M, et al. Evaluation of a potential metabolism-mediated drug-drug interaction between atomoxetine and bupropion in healthy volunteers. *J Pharm Pharm Sci.* 2016;19:198-207.
186. Belle DJ, Ernest CS, Sauer J-M, Smith BP, Thomasson HR, Witcher JW. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. *J Clin Pharmacol.* 2002;42:1219-1227.
187. Todor I, Popa A, Neag M, et al. The influence of paroxetine on the pharmacokinetics of atomoxetine and its main metabolite. *Clujul Med.* 2015;88:513-520.
188. Sauer JM, Long AJ, Ring B, et al. Atomoxetine hydrochloride: clinical drug-drug interaction prediction and outcome. *J Pharmacol Exp Ther.* 2004;308:410-418.
189. Kasi PM, Mounzer R, Gleeson GH. Side effects of atomoxetine and its interactions with inhibitors of the cytochrome P450 system. *Case Rep Med.* 2011;2011:952584.
190. Naguy A, Al-Mutairi H, Al-Tajali A. Atomoxetine-related takotsubo cardiomyopathy. *J Psychiat Pract.* 2016;22:232-233.
191. Hazell P, Becker K, Nikkanen EA, et al. Relationship between atomoxetine plasma concentration, treatment response and tolerability in attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *Atten Defic Hyperact Disord.* 2009;1:201-210.
192. Marchei E, Papaseit E, Garcia-Algar OQ, Farrè M, Pacifici R, Pichini S. Determination of atomoxetine and its metabolites in conventional and non-conventional biological matrices by liquid chromatography-tandem mass spectrometry. *J Pharmaceut Biomed.* 2012;60:26-31.
193. Papaseit E, Marchei E, Mortali C, et al. Development and validation of a liquid chromatography-tandem mass spectrometry assay for hair analysis of atomoxetine and its metabolites: application in clinical practice. *Forensic Sci Int.* 2012;218:62-67.
194. Mullen JH, Shugert RL, Ponsler GD, et al. Simultaneous quantification of atomoxetine as well as its primary oxidative and O-glucuronide metabolites in human plasma and urine using liquid chromatography tandem mass spectrometry (LC/MS/MS). *J Pharmaceut Biomed.* 2005;38:720-733.
195. Choi CI, Jang CG, Bae JW, Lee SY. Validation of an analytical LC-MS/MS method in human plasma for the pharmacokinetic study of atomoxetine. *J Anal Chem.* 2013;68:986-991.
196. Appel DI, Brinda B, Markowitz JS, Newcorn JH, Zhu H-J. A liquid chromatography/tandem mass spectrometry assay for the analysis of atomoxetine in human plasma and in vitro cellular samples. *Biomed Chromatogr.* 2012;26(11):1364-1370.
197. Stegmann B, Dörfelt A, Haen E. Quantification of methylphenidate, dexamphetamine, and atomoxetine in human serum and oral fluid by HPLC with fluorescence detection. *Ther Drug Monit.* 2016;38:98-107.
198. Tatar Ulu S. Sensitive high performance liquid chromatographic method for determination of atomoxetine in plasma and urine precolumn derivatization with 1-dimethylaminonaphthalene-5-sulphonyl chloride. *J Liq Chromatogr.* 2012;35:747-756.
199. Zhu H-J, Wang J-S, Donovan JL, DeVane CL, Gibson BB, Markowitz JS. Sensitive quantification of atomoxetine in human plasma by HPLC with fluorescence detection using 4-(4,5-diphenyl-1H-imidazole-2-yl) benzoyl chloride derivatization. *J Chromatogr B.* 2007;846:351-354.
200. Guo W, Li W, Guo G, et al. Determination of atomoxetine in human plasma by a high performance liquid chromatographic method with ultraviolet detection using liquid-liquid extraction. *J Chromatogr B.* 2007;854:128-134.
201. Patel C, Patel M, Rani S, Nivsarkar M, Padh HA. New high performance liquid chromatographic method for quantification of atomoxetine in human plasma and its application for pharmacokinetic study. *J Chromatogr B.* 2007;850(1-2):356-360.
202. Kashani J, Ruha A-M. Isolated atomoxetine overdose resulting in seizure. *J Emerg Med.* 2007;32:175-178.
203. Garside D, Ropero-Miller JD, Riemer EC. Postmortem tissue distribution of atomoxetine following fatal and nonfatal doses - three case reports. *J Forensic Sci.* 2006;51:179-182.
204. Zeng H-J, Yang R, Zhang Y, Li J-J, Qu L-B. Capillary electrophoresis coupled with electrochemiluminescence for determination of atomoxetine hydrochloride and the study on its interactions with three proteins. *Luminescence.* 2015;30:124-130.

205. Kalgutkar AS, Vaz ADN, Lame ME, et al. Hop CECA. Bioactivation of the nontricyclic antidepressant nefazodone to a reactive quinone-imine species in human liver microsomes and recombinant cytochrome P450 3A4. *Drug Metab Dispos.* 2005;33:243-253.
206. Li AC, Shou WZ, Mai TT, Jiang X-Y. Complete profiling and characterization of in vitro nefazodone metabolites using two different tandem mass spectrometric platforms. *Rapid Commun Mass Spectrom.* 2007;21:4001-4008.
207. Mayol RF, Cole CA, Luke GM, Colson KL, Kerns EH. Characterization of the metabolites of the antidepressant drug nefazodone in human urine and plasma. *Drug Metab Dispos.* 1994;22:304-311.
208. Mercolini L, Colliva C, Amore M, Fanali S, Raggi MA. HPLC analysis of the antidepressant trazodone and its main metabolite m-CPP in human plasma. *J Pharmaceut Biomed.* 2008;47:882-887.
209. Rotzinger S, Baker GB. Human CYP3A4 and the metabolism of nefazodone and hydroxynefazodone by human liver microsomes and heterologously expressed enzymes. *Eur Neuropsychopharmacol.* 2002;12:91-100.
210. Von Moltke LL, Zalma A, Granda BW, Grassi JM, Shader RI, Greenblatt DJ. Meta-chloro-phenylpiperazine (mCPP): P450-3A-dependent formation from nefazodone and trazodone; P450-2D6-dependent clearance. *Clin Pharm Ther.* 1999;65:144. -144.
211. Preskorn SH, Catterson ML. General principles of pharmacokinetics. In: Preskorn SH, Stanga CY, Feighner JP, Ross R, eds. *Antidepressants: Past, Present and Future.* Berlin and Heidelberg: Springer; 2004.
212. DeVane CL, Donovan JL, Liston HL, et al. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol.* 2004;24:4-10.
213. Abernethy DR, Barbey JT, Franc J, et al. Loratadine and terfenadine interaction with nefazodone: both antihistamines are associated with QTc prolongation. *Clin Pharm Ther.* 2001;69:96-103.
214. Kotlyar M, Brewer ER, Golding M, Carson SW. Nefazodone inhibits methylprednisolone disposition and enhances its adrenal-suppressant effect. *J Clin Psychopharmacol.* 2003;23:652-656.
215. Taylor D, Bodani M, Hubbeling A, Murray R. The effect of nefazodone on clozapine plasma concentrations. *Int Clin Psychopharmacol.* 1999;14:185-187.
216. Marino MR, Langenbacher KM, Hammett JL, Nichola P, Uderman HD. The effect of nefazodone on the single-dose pharmacokinetics of phenytoin in healthy male subjects. *J Clin Psychopharmacol.* 1997;17:27-33.
217. Dockens RC, Greene DS, Barbhaiya RH. Assessment of pharmacokinetic and pharmacodynamic drug interactions between nefazodone and digoxin in healthy male volunteers. *J Clin Pharmacol.* 1996;36:160-167.
218. Barbhaiya RH, Shukla UA, Greene DS, Breuel H-P, Midha KK. Investigation of pharmacokinetic and pharmacodynamic interactions after coadministration of nefazodone and haloperidol. *J Clin Psychopharmacol.* 1996;16:26-34.
219. Mandrioli R, Mercolini L, Raggi MA. Benzodiazepine metabolism: an analytical perspective. *Curr Drug Metab.* 2008;9:827-844.
220. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. *J Clin Psychopharmacol.* 1995;15:399-408.
221. Barbhaiya RH, Shukla UA, Kroboth PD, Greene DS. Coadministration of nefazodone and benzodiazepines: II. A pharmacokinetic interaction study with triazolam. *J Clin Psychopharmacol.* 1995;15:320-326.
222. Lam YWF, Alfaro CL, Ereshefsky L, Miller M. Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. *J Clin Pharmacol.* 2003;43(11):1274-1282.
223. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: IV. A pharmacokinetic interaction study with lorazepam. *J Clin Psychopharmacol.* 1995;15:409-416.
224. Khan AY, Preskorn SH, Horst WD. Coadministration of nefazodone and desipramine: a pharmacokinetic interaction study. *J Pak Med Ass.* 2007;57:230-235.
225. Laroudie C, Salazar DE, Cosson J-P, et al. Pharmacokinetic evaluation of co-administration of nefazodone and lithium in healthy subjects. *Eur J Clin Pharmacol.* 1999;54:923-928.
226. Marcucci C, et al, ed. *A Case Approach to Perioperative Drug-Drug Interactions.* Berlin and Heidelberg: Springer; 2015: 767.
227. Michalski LS, Bhuva D, Pakrasi A, Holt DR, Hou SH. Sirolimus and nefazodone interaction in a renal transplant patient. *Eur J Psychiat.* 2011;25:119-121.
228. Hagan JB, Erickson D, Singh RJ. Triamcinolone acetonide induced secondary adrenal insufficiency related to impaired CYP3A4 metabolism by coadministration of nefazodone. *Pain Med.* 2010;11:1132-1135.
229. Alderman CP, Gebauer MG, Gilbert AL, Condon JT. Possible interaction of zopiclone and nefazodone. *Ann Pharmacother.* 2001;35:1378-1380.
230. Yao M, Srinivas NR. Simultaneous quantitation of d7-nefazodone, nefazodone, d7-hydroxynefazodone, hydroxynefazodone, m-chlorophenylpiperazine and triazole-dione in human plasma by liquid chromatographic-mass spectrometry. *Biomed Chromatogr.* 2000;14:106-112.
231. Burke MJ, Preskorn SH. Therapeutic drug monitoring of antidepressants. In: Preskorn SH, Stanga CY, Feighner JP, Ross R, eds. *Antidepressants: Past, Present and Future.* Berlin and Heidelberg: Springer; 2004.

232. Barbhैया RH, Buch AB, Greene DS. A study of the effect of age and gender on the pharmacokinetics of nefazodone after single and multiple doses. *J Clin Psychopharmacol*. 1996;16:19-25.
233. Mao Y, Huang M-Q, Xia Y-Q, Jemal M. High-throughput quantitation of nefazodone and its metabolites in human plasma by high flow direct-injection LC-MS/MS. *J Pharmaceut Biomed*. 2007;43:1808-1819.
234. Yao M, Shah VR, Shyu WC, Srinivas NR. Sensitive liquid chromatographic-mass spectrometric assay for the simultaneous quantitation of nefazodone and its metabolites hydroxynefazodone m-chlorophenylpiperazine and triazole-dione in human plasma using single-ion monitoring. *J Chromatogr B*. 1998;718:77-85.
235. Dodd S, Buist A, Burrows GD, Maguire KP, Norman TR. Determination of nefazodone and its pharmacologically active metabolites in human blood plasma and breast milk by high-performance liquid chromatography. *J Chromatogr B*. 1999;730:249-255.
236. Franc JE, Duncan GF, Farmen RH, Pittman KA. High-performance liquid chromatographic method for the determination of nefazodone and its metabolites in human plasma using laboratory robotics. *J Chromatogr B*. 1991;570:129-138.
237. Bjork H, Bengtsson F. A simple method for routine therapeutic drug monitoring of the novel antidepressant nefazodone and its main metabolite m-chlorophenylpiperazine in serum with high-performance liquid chromatography. *Nord J Psychiat*. 1998;52:117.
238. Franklin M. Determination of nefazodone and its metabolites in plasma by high-performance liquid chromatography with coulometric detection. *J Pharmaceut Biomed*. 1993;11:1109-1113.
239. Zlotos DP. Recent progress in the development of agonists and antagonists for melatonin receptors. *Curr Med Chem*. 2012;19:3532-3549.
240. Fasipe OJ. Neuropharmacological classification of antidepressant agents based on their mechanisms of action. *Arch Med Health Sci*. 2018;6:81-94.
241. European Medicines Agency. Valdoxan (agomelatine). www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000915/human_med_001123.jsp&mid=WC0b01ac058001d124. Accessed September 10, 2019.
242. Pae C-U. Agomelatine: a new option for treatment of depression? *Exp Opin Pharmacother*. 2014;15:443-447.
243. Gahr M, Kratzer W, Fuchs M, Connemann BJ. Safety and tolerability of agomelatine: focus on hepatotoxicity. *Curr Med Chem*. 2014;15:694-702.
244. Australian Therapeutic Goods Administration. Australian Public Assessment Report for Agomelatine. <https://www.tga.gov.au/sites/default/files/auspar-valdoxan.pdf>. Accessed September 15, 2019
245. Dubocovich ML. Drug evaluation: agomelatine targets a range of major depressive disorder symptoms. *Curr Opin Investig Drugs*. 2006;7:670-680.
246. Hardeland R. Agomelatine and the risk of hepatotoxicity. *J Sympt Signs*. 2014;3341-3346.
247. Liu X, Lu Y-F, Guan X, Zhao M, Wang J, Li F. Characterizing novel metabolic pathways of melatonin receptor agonist agomelatine using metabolomic approaches. *Biochem Pharmacol*. 2016;109:70-82.
248. Saiz-Rodríguez M, Ochoa D, Belmonte C, et al. Polymorphisms in CYP1A2:CYP2C9 and ABCB1 affect agomelatine pharmacokinetics. *J Psychopharmacol*. 2019;33:522-531.
249. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26:39-67.
250. EMC, Electronic Medicines Compendium. Valdoxan 25 mg film-coated tablets. <https://www.medicines.org.uk/emc/product/6564/smpc>. Accessed September 15, 2019
251. Štuhec M. Excessive sweating induced by interaction between agomelatine and duloxetine hydrochloride: case report and review of the literature. *Wien Klin Wochensh*. 2015;127:703-706.
252. Imboden C, Hatzinger M. Agomelatine-induced akathisia with concomitant duloxetine medication: a case report. *Pharmacopsychiatry*. 2012;45:162.
253. Mercolini I, Mandrioli R, Trerè T, Bugamelli F, Ferranti A, Raggi MA. Fast CE analysis of adrenergic amines in different parts of *Citrus aurantium* fruit and dietary supplements. *J Sep Sci*. 2010;33:2520-2527.
254. Nadar JS, Kale PP, Kadu PK, Prabhavalkar K, Dhangar R. Potentiation of antidepressant effects of agomelatine and bupropion by hesperidin in mice. *Neurol Res Int*. 2018;2018:1-7.
255. Song L, Du Q, Jiang X, Wang L. Effect of CYP1A2 polymorphism on the pharmacokinetics of agomelatine in Chinese healthy male volunteers. *J Clin Pharm Ther*. 2014;39:204-209.
256. Li C, Xu J, Zheng Y, et al. Bioequivalence and pharmacokinetic profiles of agomelatine 25-mg tablets in healthy Chinese subjects: a four-way replicate crossover study demonstrating high intra- and inter-individual variations. *Chem Pharm Bull*. 2017;65:524-529.
257. Song L, Wang M, Wen A, et al. Determination of agomelatine in human plasma by LC-MS/MS: application to a pharmacokinetic study in Chinese volunteers. *J China Pharm Univ*. 2014;45:698-702.
258. Ogawa T, Iwai M, Hattori H, et al. High-throughput analysis of ramelteon, agomelatine, and melatonin in human plasma by ultra-performance liquid chromatography-tandem mass spectrometry. *Forensic Toxicol*. 2014;32:126-131.

259. Wang X, Zhang D, Liu M, et al. LC-MS/MS method for the determination of agomelatine in human plasma and its application to a pharmacokinetic study. *Biomed Chromatogr.* 2014;28:218-222.
260. Patil SR, Nerurkar KK, Kalamkar AM, Pukale V, Mangaonkar KV, Pingale SG. Validated LC-MS/MS method for quantification of agomelatine in human plasma and its application in a pharmacokinetic study. *J Mass Spectrom.* 2012; 47:23-28.
261. Cheng J, He J, Mao X, Zhou Q, Zhang M, Zhang H. Concentration determination of agomelatine in human plasma and its pharmacokinetics study. *Pharm Care Res.* 2018;18:199-202.
262. Li M, Tang F, Xie F, et al. Development and validation a LC-MS/MS method for the simultaneous determination of agomelatine and its metabolites, 7-desmethyl-agomelatine and 3-hydroxy-agomelatine in human plasma: application to a bioequivalence study. *J Chromatogr B.* 2015;1003:60-66.
263. Saracino MA, Mercolini L, Carhini G, et al. Multi-matrix assay of the first melatonergic antidepressant agomelatine by combined liquid chromatography-fluorimetric detection and microextraction by packed sorbent. *J Pharmaceut Biomed.* 2014;95:61-67.
264. Lerman C, Niaura R, Collins BN, et al. Effect of bupropion on depression symptoms in a smoking cessation clinical trial. *Psychol Addict Behav.* 2004;18:362-366.
265. Crooks PA, Bardo MT, Dwoskin LP. Nicotinic receptor antagonists as treatments for nicotine abuse. *Adv Pharmacol.* 2014;69:513-551.
266. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants: a systematic review and meta-analysis. *Drug Saf.* 2008;31:851-865.
267. Masters AR, Gufford BT, Lu JBL, Metzger IF, Jones DR, Desta Z. Chiral plasma pharmacokinetics and urinary excretion of bupropion and metabolites in healthy volunteers. *J Pharmacol Exp Ther.* 2016;358:230-238.
268. Xue C, Zhang X, Cai W. Prediction of drug-drug interactions with bupropion and its metabolites as CYP2D6 inhibitors using a physiologically-based pharmacokinetic model. *Pharmaceutics.* 2018;10:E1.
269. Benowitz NL, Zhu AZX, Tyndale RF, Dempsey D, Jacob P. Influence of CYP2B6 genetic variants on plasma and urine concentrations of bupropion and metabolites at steady state. *Pharmacogenet Genomics.* 2013;23:135-141.
270. Sager JE, Choiniere JR, Chang J, Stephenson-Famy A, Nelson WL, Isoherranen N. Identification and structural characterization of three new metabolites of bupropion in humans. *ACS Med Chem Lett.* 2016;7:791-796.
271. Hesse LM, Venkatakrishnan K, Court MH, et al. CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants. *Drug Metab Dispos.* 2000;28:1176-1183.
272. Paslakis G, Gilles M, Deuschle M. Clinically relevant pharmacokinetic interaction between venlafaxine and bupropion: a case series. *J Clin Psychopharmacol.* 2010;30:473-474.
273. Nirogi R, Palacharla RC, Mohammed AR, Manoharan A, Ponnamaneni RK, Bhyrapuneni G. Evaluation of metabolism dependent inhibition of CYP2B6 mediated bupropion hydroxylation in human liver microsomes by monoamine oxidase inhibitors and prediction of potential as perpetrators of drug interaction. *Chem-Biol Interact.* 2015;230:9-20.
274. Sager JE, Tripathy S, Price LS, et al. In vitro to in vivo extrapolation of the complex drug-drug interaction of bupropion and its metabolites with CYP2D6; simultaneous reversible inhibition and CYP2D6 downregulation. *Biochem Pharmacol.* 2017;123:85-96.
275. Reese MJ, Wurm RM, Muir KT, et al. An in vitro mechanistic study to elucidate the desipramine/bupropion clinical drug-drug interaction. *Drug Metab Dispos.* 2008;36:1198-1201.
276. Popli AP, Tanquary J, Lamparella V, Masand PS. Bupropion and anticonvulsant drug interactions. *Ann Clin Psychiat.* 1995;7:99-101.
277. Hsyu P-H, Singh A, Giargiari TD, Johnston JA. Pharmacokinetics of bupropion and its metabolites in smokers and non-smokers. *Clin Pharm Ther.* 1997;61:180-183.
278. Hesse LM, Von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: Potential drug interactions with bupropion. *Drug Metab Dispos.* 2001;29:100-102.
279. McCollum DL, Greene JL, McGuire DK. Severe sinus bradycardia after initiation of bupropion therapy: a probable drug-drug interaction with metoprolol. *Cardiovasc Drug Ther.* 2004;18:329-330.
280. Shad MU, Preskorn SH. A possible bupropion and imipramine interaction. *J Clin Psychopharmacol.* 1997;17:118-119.
281. Weintraub D. Nortriptyline toxicity secondary to interaction with bupropion sustained-release. *Depress Anxiety.* 2001; 13:50-52.
282. Chandler P, Herxheimer A. Unexpected aggressive behaviour: interaction of bupropion and alcohol. *Int J Risk Saf Med.* 2011;23:133-137.
283. Marcucci C, et al, ed. *A Case Approach to Perioperative Drug-Drug Interactions.* Berlin and Heidelberg: Springer; 2015: 543.
284. Schmid Y, Rickli A, Schaffner A, et al. Interactions between bupropion and 3,4-methylenedioxyamphetamine in healthy subjects. *J Pharmacol Exp Ther.* 2015;353:102-111.

285. Lewis BR, Aoun SL, Bernstein GA, Crow SJ. Pharmacokinetic interactions between cyclosporine and bupropion or methylphenidate. *J Child Adolesc Psychopharmacol*. 2001;11:193-198.
286. Molnari JC, Hassan HE, Moeller BM, Myers AL. Drug interaction study between bupropion and ticlopidine in male CF-1 mice. *Biol Pharm Bull*. 2011;34:447-451.
287. Wang J-S, DeVane CL, Gibson BB, Donovan JL, Markowitz JS, Zhu HJ. Population pharmacokinetic analysis of drug-drug interactions among risperidone, bupropion, and sertraline in CF1 mice. *Psychopharmacology*. 2006;183:490-499.
288. Tekle A, Al-Khamis KI. Phenytoin-bupropion interaction: effect on plasma phenytoin concentration in the rat. *J Pharm Pharmacol*. 1990;42:799-801.
289. Shen Y, Yu Y, Lai W, et al. Evaluation of a potential clinical significant drug-drug interaction between digoxin and bupropion in cynomolgus monkeys. *Pharm Res*. 2019;36.
290. He J, Yu Y, Prasad B, Chen X, Unadkat JD. Mechanism of an unusual, but clinically significant, digoxin-bupropion drug interaction. *Biopharm Drug Dispos*. 2014;35:253-263.
291. Abrudan MB, Muntean DM, Gheldiu AM, Neag MA, Vlase L. The pharmacokinetic interaction study between carvedilol and bupropion in rats. *Pharmacology*. 2017;99:139-143.
292. Gheldiu A-M, Popa A, Neag M, et al. Assessment of a potential pharmacokinetic interaction between nebivolol and bupropion in healthy volunteers. *Pharmacology*. 2016;98:190-198.
293. Johnston JA, Fiedler-Kelly J, Glover ED, Sachs DP, Grasela TH, DeVeauugh-Geiss J. Relationship between drug exposure and the efficacy and safety of bupropion sustained release for smoking cessation. *Nicotine Tob Res*. 2001;3:131-140.
294. Park S, Park C-S, Lee SJ, et al. Development and validation of a high-performance liquid chromatography-tandem mass spectrometric method for simultaneous determination of bupropion, quetiapine and escitalopram in human plasma. *Biomed Chromatogr*. 2015;29:612-618.
295. Parekh JM, Sutariya DK, Vaghela RN, Sanyal M, Yadav M, Shrivastav PS. Sensitive, selective and rapid determination of bupropion and its major active metabolite, hydroxybupropion, in human plasma by LC-MS/MS: application to a bioequivalence study in healthy Indian subjects. *Biomed Chromatogr*. 2012;26:314-326.
296. Yeniceci D, Dogrukol-Ak D, An LC. Method for the determination of bupropion and its main metabolite, hydroxybupropion in human plasma. *Chromatographia*. 2009;70:1703-1708.
297. Shahi PK, Patel H, Shah V, Bhokari A, Thennati R, Ameta R. Simultaneous quantitative determination of bupropion and its metabolites by high performance liquid chromatography tandem mass spectrometry detection: application to bioequivalence study. *Indian J Pharm Ed Res*. 52, 2018:S37-S46.
298. Shah PA, Parekh JM, Shrivastav PS. Assessment of critical extraction and chromatographic parameters for the determination of bupropion and its three primary metabolites in human plasma by LC-MS/MS. *Microchem J*. 2017;135:81-90.
299. Borges V, Yang E, Dunn J, Henion J. High-throughput liquid chromatography-tandem mass spectrometry determination of bupropion and its metabolites in human, mouse and rat plasma using a monolithic column. *J Chromatogr B*. 2004;804:277-287.
300. Masters AR, McCoy M, Jones DR, Desta Z. Stereoselective method to quantify bupropion and its three major metabolites, hydroxybupropion, erythro-dihydrobupropion, and threo-dihydrobupropion using HPLC-MS/MS. *J Chromatogr B*. 2016;1015-1016:201-208.
301. Teitelbaum AM, Flaker AM, Kharasch ED. Development, validation and application of a comprehensive stereoselective LC/MS-MS assay for bupropion and oxidative, reductive, and glucuronide metabolites in human urine. *J Chromatogr B*. 2016;1027:239-253.
302. Burleson Daviss W, Perel JM, Brent DA, et al. Acute antidepressant response and plasma levels of bupropion and metabolites in a pediatric-aged sample: an exploratory study. *Ther Drug Monit*. 2006;28:190-198.
303. Loboz KK, Gross AS, Ray J, McLachlan AJ. HPLC assay for bupropion and its major metabolites in human plasma. *J Chromatogr B*. 2005;823:115-121.
304. Tatar Ulu S, Tuncel M. Determination of bupropion using liquid chromatography with fluorescence detection in pharmaceutical preparations, human plasma and human urine. *J Chromatogr Sci*. 2012;50:433-439.
305. Petrides AK, Moskowitz J, Johnson-Davis KL, et al. The development and validation of a turbulent flow-liquid chromatography-tandem mass spectrometric method for the simultaneous quantification of citalopram, sertraline, bupropion and hydroxybupropion in serum. *Clin Biochem*. 2014;47:73-79.
306. Wang X, Vernikovskaya DI, Abdelrahman DR, Hankins GDV, Ahmed MS, Nanovskaya TN. Simultaneous quantitative determination of bupropion and its three major metabolites in human umbilical cord plasma and placental tissue using high-performance liquid chromatography-tandem mass spectrometry. *J Pharmaceut Biomed*. 2012;70:320-329.
307. Paul R, Schaaff N, Padberg F, Möller HJ, Frodl T. Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: report of two cases. *World J Biol Psychiat*. 2009;10:241-244.
308. Shouan A, Grover S. Adjunctive intranasal esketamine in treatment-resistant depression. *JAMA Psychiat*. 2018;75:654.

309. European Medicines Agency. List of nationally authorised medicinal products – active substance: esketamine. https://www.ema.europa.eu/en/documents/psusa/esketamine-list-nationally-authorized-medicinal-products-psusa/00001266/201608_en.pdf. Accessed September 15, 2019
310. USA Food and Drug Administration. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified>. Accessed September 15, 2019
311. Hashimoto K. Rapid-acting antidepressant ketamine, its metabolites and other candidates: a historical overview and future perspective. *Psychiatry Clin Neurosci*. 2019;73:613-627.
312. Ficek J, Zygmunt M, Piechota M, et al. Molecular profile of dissociative drug ketamine in relation to its rapid antidepressant action. *BMC Genomics*. 2016;17:362.
313. Janssen Inc. Spravato Prescribing Information. <https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf>. Accessed September 10, 2019.
314. Hashimoto K, Yang C. Is (S)-norketamine an alternative antidepressant for esketamine? *Eur Arch Psychiatr Clin Neurosci*. 2019;269:867-868.
315. Fanta S, Kinnunen M, Backman JT, Kalso E. Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. *Eur J Clin Pharmacol*. 2015;71:441-447.
316. Ashraf MW, Peltoniemi MA, Olkkola KT, Neuvonen PJ, Saari TI. Semimechanistic population pharmacokinetic model to predict the drug–drug interaction between S-ketamine and ticlopidine in healthy human volunteers. *Pharmacometrics Syst Pharmacol*. 2018;7:687-697.
317. Peltoniemi MA, Saari TI, Hagelberg NM, Laine K, Neuvonen PJ, Olkkola KT. St John's wort greatly decreases the plasma concentrations of oral S-ketamine. *Fund Clin Pharmacol*. 2012;26:743-750.
318. Hu J-P, Chen H, Li Y. Effect of S(+)-ketamine on liver microsomal cytochrome P450 isozymes in rats. *Chin Pharm J*. 2008;43:906-909.
319. European Medicines Agency (EMA) – Committee for Medicinal Products for Human Use (CHMP), Assessment report: Spravato – Procedure No. EMEA/H/C/004535/0000. https://www.ema.europa.eu/en/documents/assessment-report/spravato-epar-public-assessment-report_en.pdf. Accessed January 31, 2020.
320. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Enantioselective pharmacokinetics of (R)- and (S)-ketamine after a 5-day infusion in patients with complex regional pain syndrome. *Chirality*. 2011;23:138-143.
321. Fassauer GM, Hofstetter R, Hasan M, et al. Ketamine metabolites with antidepressant effects: Fast, economical, and eco-friendly enantioselective separation based on supercritical-fluid chromatography (SFC) and single quadrupole MS detection. *J Pharmaceut Biomed*. 2017;146:410-419.
322. Samuels BA, Nautiyal KM, Kruegel AC, et al. The behavioral effects of the antidepressant tianeptine require the mu-opioid receptor. *Neuropsychopharmacology*. 2017;42:2052-2063.
323. Uzbekov MG. Antidepressant action of tianeptine is connected with acceleration of serotonin turnover in the synapse: a hypothesis. *Neuropsychopharmacol Hung*. 2009;11:83-87.
324. Wlaź P, Kasperek R, Wlaź A, et al. NMDA and AMPA receptors are involved in the antidepressant-like activity of tianeptine in the forced swim test in mice. *Pharmacol Rep*. 2011;63:1526-1532.
325. Grislain L, Gele P, Bertrand M, et al. The metabolic pathways of tianeptine, a new antidepressant, in healthy volunteers. *Drug Metab Dispos*. 1990;18:804-808.
326. Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs*. 1995;49:411-439.
327. Toon S, Holt BL, Langley SJ, et al. Pharmacokinetic and pharmacodynamic interaction between the antidepressant tianeptine and oxazepam at steady-state. *Psychopharmacology*. 1990;101:226-232.
328. Salvadori C, Ward C, Defrance R, Hopkins R. The pharmacokinetics of the antidepressant tianeptine and its main metabolite in healthy humans – influence of alcohol co-administration. *Fund Clin Pharmacol*. 1990;4:115-125.
329. Zini R, Morin D, Salvadori C, Tillement JP. The influence of various drugs on the binding of tianeptine to human plasma proteins. *Int J Clin Pharmacol Ther Toxicol*. 1991;29:64-66.
330. Borowicz KK, Banach M, Piskorska B, Czuczwar SJ. Effect of acute and chronic tianeptine on the action of classical antiepileptics in the mouse maximal electroshock model. *Pharmacol Rep*. 2013;65:379-388.
331. Grasela TH, Fiedler-Kelly JB, Salvadori C, Marey C, Jochensen R, Loo H. Predictive performance of population pharmacokinetic parameters of tianeptine as applied to plasma concentrations from a post-marketing study. *Eur J Clin Pharmacol*. 1993;45:123-128.
332. Szafarz M, Wencel A, Pocięcha K, Fedak FA, Wlaź P, Wyska E. Pharmacokinetic study of tianeptine and its active metabolite MC5 in rats following different routes of administration using a novel liquid chromatography tandem mass spectrometry analytical method. *N-S Arch Pharmacol*. 2018;391:185-196.

333. Zheng R, Kim B-H. Pharmacokinetic and bioequivalence assessment of two formulations of tianeptine sodium in healthy male volunteers. *Int J Clin Pharm Ther.* 2014;52:817-823.
334. Tatar Ulu S. Determination of tianeptine in human plasma using high-performance liquid chromatography with fluorescence detection. *J Chromatogr B.* 2006;834:62-67.
335. Gaulier J-M, Marquet P, Lacassie E, Desroches R, Lachatre G. High-performance liquid chromatographic determination of tianeptine in plasma applied to pharmacokinetic studies. *J Chromatogr B.* 2000;748:407-414.
336. Nicot G, Lachatre G, Gonnet C, Mallon J, Mocaer E. Ion-pair extraction and high-performance liquid chromatographic determination of tianeptine and its metabolites in human plasma, urine and tissues. *J Chromatogr B.* 1986;381:115-126.
337. Gilchrist EEA, Sadler DW. The role of depression in unnatural death: a case-based retrospective study. *J Affect Disord.* 2019;259:7-14.
338. Gartlehner G, Hansen RA, Morgan LC, et al. *Second-generation antidepressants in the pharmacologic treatment of adult depression: an update of the 2007 comparative effectiveness review.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2011. <http://www.ncbi.nlm.nih.gov/books/NBK83442/>. Accessed October 10, 2019.

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