

Trazodone Is Metabolized to *m*-Chlorophenylpiperazine by CYP3A4 from Human Sources

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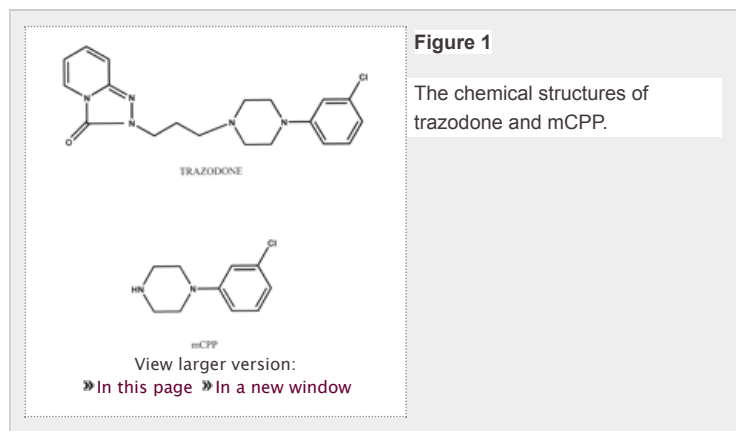
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Abstract

The metabolism of the antidepressant drug trazodone to its active metabolite, *m*-chlorophenylpiperazine (mCPP), was studied *in vitro* using human liver microsomal preparations and cDNA-expressed human cytochrome P450 (P450) enzymes. The kinetics of mCPP formation from trazodone were determined, and three *in vitro* experiments were performed to identify the major P450 enzyme involved. Trazodone (100 μ M) was incubated with 16 different human liver microsomal preparations characterized for activities of 7 different P450 isoforms. The production of mCPP correlated significantly with activity of cytochrome P4503A4 (CYP3A4) only. Trazodone (100 μ M) was then incubated with microsomes from cells expressing human CYP1A1, CYP1A2, CYP2C8, CYP2C9arg, CYP2C9cys, CYP2C19, CYP2D6, or CYP3A4. Only incubations with CYP3A4 resulted in mCPP formation. In the third experiment, the CYP3A4 inhibitor ketoconazole was found to inhibit mCPP formation concentration dependently in both human liver microsomes and in microsomes from cells expressing human CYP3A4. The present results indicate that trazodone is a substrate for CYP3A4, that CYP3A4 is a major isoform involved in the production of mCPP from trazodone, and that there is the possibility of drug-drug interactions with trazodone and other substrates, inducers and/or inhibitors of CYP3A4.

Adverse pharmacokinetic drug interactions may occur when drugs that are substrates, inducers and/or inhibitors of the same cytochrome P450 (P450)² enzymes are co-administered, potentially altering the expected rate of metabolism of one or both compounds. The clinical consequences can range from a lack of therapeutic efficacy to severe toxicity and, in extreme cases, fatality. Therefore, it is important to identify the major enzymes involved in the metabolism of a drug so that such interactions can be predicted and avoided.

Trazodone is a triazolopyridine antidepressant drug (fig.1), which is thought to act through combined 5-HT₂ antagonism and 5-HT reuptake blockade (Hara *et al.*, 1994). It is often co-prescribed with other antidepressants as a sleep-inducing agent because of its sedative side effects (Fabre, 1990; Jacobsen, 1990; Nierenberg *et al.*, 1994) or as an augmentation strategy (Maes *et al.*, 1997). This co-prescription introduces the potential for metabolic drug interactions.



Trazodone is extensively metabolized in the liver by hydroxylation, dealkylation, and *N*-oxidation (Baiocchi *et al.*, 1974; Yamato, 1974a). The active metabolite mCPP is formed by *N*-dealkylation of the piperazinyl nitrogen (Melzack *et al.*, 1979; Yamato *et al.*, 1974b). The metabolite mCPP is of interest because it has 5-HT_{2C} agonistic and 5-HT_{2A} antagonistic properties (Conn and Sanders-Bush, 1987; Fiorella *et al.*, 1995), as well as behavioral effects that are consistent with 5-HT agonistic properties such as worsening of psychoses in humans and anxiogenesis and anorexia in animals and humans (Kahn and Wetzler, 1991). It has also been suggested by some that mCPP may contribute to the antidepressant efficacy of trazodone (Maes, 1997). Therefore, a drug interaction that alters the production of mCPP could have clinically significant effects.

Current information available on the metabolism of trazodone by the P450 enzymes comes mainly from drug interaction studies, which provide only suggestive evidence of the enzymes involved and do not examine specific metabolic pathways, whether it is the parent compound or a metabolite causing the interaction or whether the interaction is competitive or non-competitive. For example, thioridazine, a CYP2D6 inhibitor, increases plasma concentrations of both trazodone and mCPP, suggesting that both are substrates for CYP2D6 but providing no information as to which metabolic pathways are involved (Yasui *et al.*, 1995). Plasma levels of trazodone, but not mCPP, are lower in smokers than in non-smokers, suggesting a possible role of the smoking-inducible CYP1A2 in trazodone, but not mCPP, metabolism (Ishida *et al.*, 1995). Carbamazepine, a CYP3A4 inducer and substrate, decreases plasma concentrations of both trazodone and mCPP, but mCPP to a lesser extent (Otani *et al.*, 1996). Clinical interactions between trazodone and fluoxetine have been reported in the form of adverse side effects such as headaches, dizziness, and excessive sedation (Metz and Shader, 1990; Nierenberg *et al.*, 1992), as well as increased plasma levels of trazodone (Aranow *et al.*, 1989; Maes *et al.*, 1997) and mCPP (Maes *et al.*, 1997). However, the causes of the interactions cannot easily be determined, as both fluoxetine and its main metabolite norfluoxetine are inhibitors of both CYP2D6 and CYP3A4 (Crewe *et al.*, 1992; Greenblatt *et al.*, 1996).

A detailed *in vitro* investigation is thus necessary to identify the individual enzymes involved in the various interactions of trazodone. In particular, the pathway leading to the formation of mCPP from trazodone is of interest given the psychopharmacological effects of this metabolite. Several *in vitro* methods are routinely used to identify the P450 enzymes involved in the oxidation of compounds (e.g. Guengerich, 1996; Iwatsubo *et al.*, 1997). The current experiments were designed to directly identify the major P450 enzymes involved in the metabolism of trazodone to mCPP using human liver microsomal preparations and cDNA-expressed human P450 enzymes.

Materials and Methods

Chemicals.

Trazodone and mCPP were purchased from RBI (Natick, MA) and Sigma (St. Louis, MO), respectively. The HCl salt of the internal standard *p*-chlorophenylethylamine was synthesized in our laboratory. Pentafluorobenzoyl chloride was purchased from Aldrich (Milwaukee, WI), glass-distilled toluene from BDH (Toronto), and potassium carbonate from Fisher Scientific (Nepean, Ontario). The components of the NADPH-generating system, namely β -nicotinamide adenine dinucleotide phosphate, glucose 6-phosphate, glucose 6-phosphate dehydrogenase, and MgCl₂, were all obtained from Sigma. Potassium phosphate monobasic and potassium phosphate dibasic (J.T. Baker) were used to prepare a solution of 0.1 M potassium phosphate buffer (pH 7.4).

Microsomal Preparations.

Microsomal preparations from metabolically competent cell lines expressing human CYP1A1, CYP1A2, CYP2C8, CYP2C9arg, CYP2C9cys, CYP2C19, CYP2D6, or CYP3A4 were purchased from Gentest (Woburn, MA).

Human liver microsomes characterized for protein content and enzyme activities were obtained from the International Institute for the Advancement of Medicine (Exton, PA).

Incubation Conditions.

The drug metabolism experiments were carried out in a volume of 100 μ l in 1.5-ml

polypropylene microcentrifuge tubes (Fisher). The incubation medium consisted of 25 μ l of an NADPH-generating system [final concentration in 100 μ l of 1 mg/ml β -nicotinamide adenine dinucleotide phosphate, 1 mg/ml glucose 6-phosphate, 0.4 U/ml glucose 6-phosphate dehydrogenase, and 0.66 mg/ml $MgCl_2$ in 0.1 M potassium phosphate buffer (pH 7.4), 10 μ l of microsomal enzyme preparation (1.5 mg microsomal protein/ml incubation mixture), 50 μ l of trazodone solution in 0.1 M potassium phosphate buffer, and 15 μ l 0.1 M potassium phosphate buffer (pH 7.4)]. The tubes were incubated for 10 min at 37°C in a water bath (Fisher Isotemp hot water bath). The incubation time was chosen based on preliminary experiments showing that the formation of mCPP was linear within the first 20 min of incubation time. Following the incubation period, the tubes were placed on ice, and 100 μ l of ice-cold 25% potassium carbonate solution was added to terminate metabolism.

Assay Procedure for mCPP.

To the basified incubation mixture, 300 μ l of double distilled H_2O (dd H_2O) and 1000 ng of the internal standard (*p*-chlorophenylethylamine, in 100 μ l dd H_2O) were added. The incubation mixtures were then transferred to screw cap culture tubes (Fisher, 160 mm \times 15 mm), and mCPP was extracted and derivatized by shaking the tubes for 15 min on an Ika Vibrex VXR vortex mixer (Janke & Kunkel, Staufen, Germany) with 2 ml of a solution of toluene and pentafluorobenzoyl chloride in a ratio of 100:1. The tubes were then centrifuged at 1000g for 5 min in a benchtop centrifuge (Sorvall GLC-2B general laboratory centrifuge, DuPont, Wilmington, DE). The organic phase was pipetted to 100 \times 13-mm screw cap culture tubes and taken to dryness in a Savant evaporator (Speed Vac SC 110, Fisher). The residue was reconstituted in 150 μ l of toluene for gas chromatographic analysis.

Instrumental Analysis.

A 1- μ l aliquot of the solution in toluene was injected on a Hewlett-Packard (HP) model 5890 gas chromatograph equipped with a nitrogen-phosphorus detector and linked to an HP 3392A integrator. A 15-m fused silica capillary column (internal diameter of 0.25 mm) coated with a 0.25- μ m film thickness of 5% phenylmethyl polysiloxane was used. The carrier gas was helium at a flow rate of 3.5 mL/min, and the make-up gas was helium at a flow rate of 30 mL/min. Hydrogen and air were used at flow rates of 4 and 80 mL/min, respectively. The oven temperature was set at 105°C for an initial time of 0.5 min and was then set to increase at a rate of 12°C/min to a final temperature of 295°C. The injection port temperature was set at 270°C, and the detector temperature was 325°C. All injections were in the splitless mode with a purge off time of 0.5 min.

Determination of the Kinetic Constants for mCPP Formation from Trazodone.

The kinetic constants of K_M and V_{max} were estimated for the formation of mCPP from trazodone by incubating varying concentrations of trazodone (450, 300, 200, 133, 88.89, 59.26, 39.51, 26.34, 17.56, 11.71, 7.80, 5.20, 3.47, 2.31, and 0 μ M) with human liver microsomes under the conditions described above. The data were analyzed by iterative nonlinear least squares regression analysis (GraphPad Prism), fitting the data to the equation $v = (V_{max} \cdot S) / (K_M + S)$, where v is the reaction velocity corresponding to S , the substrate concentration (trazodone), V_{max} is the maximal velocity, and K_M is the substrate concentration at which the reaction velocity equals 50% of V_{max} .

Correlations with P450 Enzyme Activities in a Panel of Human Liver Microsomal Preparations.

Trazodone (100 μ M final concentration) was incubated with the NADPH-generating system and microsomes prepared from a panel of 16 human livers characterized for their catalytic activity for CYP1A2 (phenacetin O-deethylation), CYP2A6 (coumarin 7-hydroxylation), CYP2C19 (mephenytoin 4-hydroxylation), CYP2D6 (dextromethorphan O-demethylation), CYP2E1 (chlorzoxazone 6-hydroxylation), CYP3A4 (6-hydroxylation of [^{14}C]testosterone), and CYP4A11 (omega-hydroxylation of [^{14}C]lauric acid). The rate of formation of mCPP was then correlated with the activities of the specific enzymes for each of the 16 human livers (GraphPad Prism).

Incubations with Single Expressed Enzymes.

Trazodone (100 μ M final concentration, added in a volume of 50 μ l) was incubated in the NADPH-generating system (25 μ l), potassium phosphate buffer (15 μ l), and 10 μ l of a microsomal preparation (1 mg microsomal protein/ml incubation mixture) expressing CYP1A1, CYP1A2, CYP2C8, CYP2C9arg, CYP2C9cys, CYP2C19, CYP2D6, or CYP3A4 for 30 min. These incubations were repeated in four separate experiments.

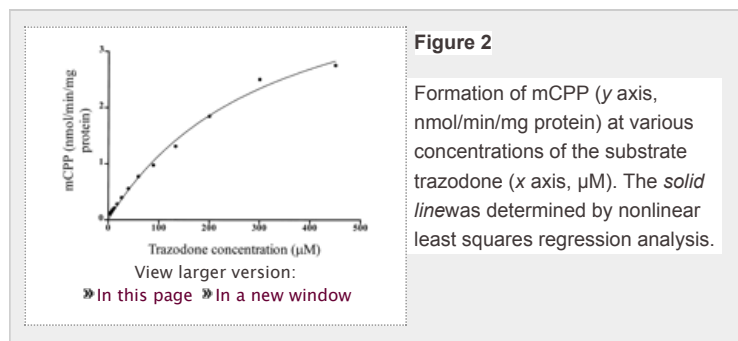
Inhibition with Ketoconazole.

The CYP3A4 inhibitor ketoconazole (final concentrations in 100 μ l of 6.4, 3.2, 1.6, 0.8, 0.4, 0.2, and 0.0 μ M, added in 10 μ l of buffer) was pre-incubated for 10 min with 25 μ l of the NADPH-generating system, 5 μ l of potassium phosphate buffer, and 10 μ l of either human liver microsomes (1.5 mg of microsomal protein/ml incubation mixture) or microsomes from cells expressing human CYP3A4 (1 mg of microsomal protein/ml incubation mixture). Trazodone (100 μ M final concentration, added in a volume of 50 μ L) was then added, and the incubation was continued for a further 10 min. As a control, quinidine, a specific inhibitor of CYP2D6, was also incubated as described for ketoconazole, using concentrations of 6.0, 3.0, 1.5, 0.75, 0.375, and 0 μ M. The inhibitions were repeated in three separate experiments.

Results

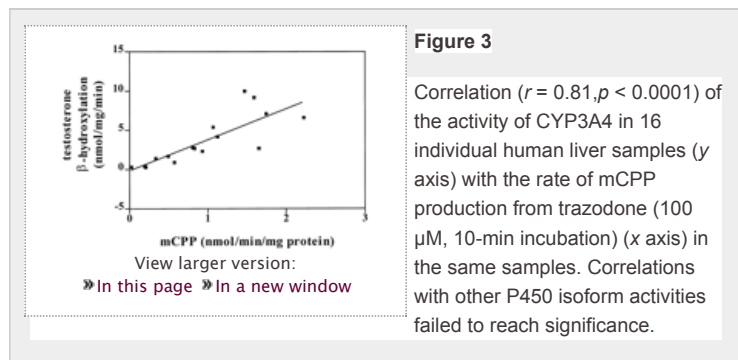
Kinetic Analyses.

Incubations of various concentrations of trazodone with human liver microsomes resulted in a concentration-dependent formation of mCPP, as shown in fig. 2. The apparent K_M was 311.3 ± 32.19 μ M, and apparent V_{max} was 4.95 ± 0.29 nmol/min/mg protein.



Correlations with P450 Enzyme Activities in a Panel of Human Liver Microsomal Preparations.

The rate of formation of mCPP showed significant correlation ($r = 0.81$, $p < 0.0001$) with CYP3A4 activity (fig. 3). Correlations with all other P450 enzymes failed to reach significance (CYP1A2, $r = 0.27$, $p = 0.32$; CYP2A6, $r = 0.47$, $p = 0.07$; CYP2C19, $r = 0.16$, $p = 0.55$; CYP2D6, $r = 0.41$, $p = 0.11$; CYP2E1, $r = 0.40$, $p = 0.13$; CYP4A11, $r = 0.33$, $p = 0.21$).



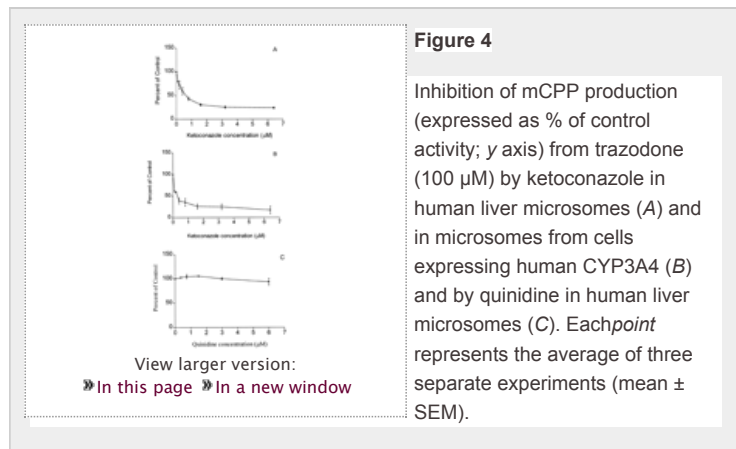
Incubations with Single Expressed Enzymes.

Trazodone incubations with microsomes from cells expressing only CYP3A4 resulted in mCPP production (0.3903 ± 0.0631 nmol/min/mg protein, $N = 4$), whereas incubations with

microsomes from cells expressing only CYP1A1, CYP1A2, CYP2C8, CYP2C9arg, CYP2C9cys, CYP2C19, or CYP2D6 did not result in detectable mCPP formation.

Inhibition with Ketoconazole.

The CYP3A4 inhibitor ketoconazole resulted in a concentration-dependent inhibition of mCPP production in microsomes from both human liver and cells expressing human CYP3A4 (fig. 4). Incubations with quinidine did not inhibit mCPP formation (fig. 4).



Discussion

The present experiments showed that mCPP production from trazodone is correlated with CYP3A4 activity in human liver microsomes, is formed from incubations with microsomes from cells expressing CYP3A4 only, and is diminished in the presence of an inhibitor of CYP3A4. Taken together, these results indicate strongly that trazodone is a substrate of CYP3A4 and that this P450 enzyme is important in the formation of the metabolite mCPP. Therefore, there is the potential for drug-drug interactions with this drug and other substrates, inhibitors, and/or inducers of CYP3A4.

Plasma levels of trazodone show wide interindividual differences and typically range from about 0.38 to 5.8 μ M (Vatassery *et al.*, 1997). However, it is not the plasma concentration that is relevant but rather the concentration at the enzyme site, or the hepatic concentration, which is of importance with respect to drug interactions (Harvey and Preskorn, 1995; Preskorn, 1996; von Moltke *et al.*, 1996). Lipophilic drugs partition extensively into the liver, and liver/water partition ratios are typically used to estimate liver drug concentrations (Greenblatt *et al.*, 1996). The hepatic extraction ratio for trazodone is not currently known, but if it is assumed to have a partition ratio similar to the selective serotonin reuptake inhibitors, which are also highly lipophilic and have hepatic extraction ratios of 12 to 26 (Harvey and Preskorn, 1995; Schmider *et al.*, 1996), then hepatic concentrations of trazodone can be expected to range from 60 to 100 μ M at a plasma concentration of 5 μ M. Therefore, the concentration of trazodone used in the present experiments can be considered to be clinically relevant. Furthermore, as the concentration of 100 μ M trazodone is within the linear range of metabolite formation, kinetic parameters should be constant and thus are applicable to lower trazodone concentrations (Iwatsubo *et al.*, 1997).

The clinical significance of potential drug interactions with trazodone depends upon several factors. First, it is important to distinguish between interactions resulting from trazodone's effects on other compounds and interactions resulting from the effects of other compounds on trazodone. When considering the effects of trazodone on other compounds, it is important to note that the present experiments showed that trazodone is a substrate of CYP3A4 and therefore may act as a competitive inhibitor of other CYP3A4 substrates. The consequences of this interaction will depend upon the relative affinities and concentrations of trazodone and the competing drug at the enzyme, as well as the therapeutic index of both drugs. The therapeutic index of the interacting drug is important, as clinically significant interactions with a CYP3A4 substrate with a narrow therapeutic index, such as terfenadine, could result (Wilkinson, 1996).

The second type of interaction that may occur is from the effects of other compounds on trazodone metabolism. Although trazodone has a relatively wide therapeutic index, it does have potentially bothersome or dangerous side effects such as excessive sedation, which could become a problem at higher plasma concentrations (Haria *et al.*, 1994). However, the most important consideration with respect to trazodone metabolism is the ability to maintain therapeutic plasma concentrations. Clinical antidepressant response is significantly correlated with steady-state plasma trazodone concentrations, and a threshold concentration of 650 ng/ml is considered necessary for antidepressant response (Monteleone *et al.*, 1989). Therefore, any factor that results in a lowering of plasma trazodone levels may interfere with the clinical efficacy of the drug. Because CYP3A4 levels vary 5–20-fold between individuals (Wilkinson, 1996) and because CYP3A4 is inhibited and induced by many commonly encountered drugs and environmental compounds (von Moltke *et al.*, 1995; Wilkinson, 1996), it is important to be aware that trazodone is a substrate of CYP3A4 and thus subject to many factors that may alter its plasma concentration. The clinical significance of this potential interaction has already been noted with carbamazepine, a CYP3A4 inducer, which decreased plasma trazodone levels (Otani *et al.*, 1996). The extent of any interaction with trazodone will of course depend upon individual differences in CYP3A4 activity, as well as plasma levels of both trazodone and the interacting drug. However, as therapeutic concentrations of trazodone are typically below its K_M , it is subject to first-order kinetics and as such is highly sensitive to changes in the concentration of enzyme or substrate (Iwatsubo *et al.*, 1997). The high K_M value found in the present experiments for trazodone transformation is consistent with the linear pharmacokinetics of trazodone and mCPP seen clinically (Nilsen *et al.*, 1993). Therefore, the potential for interactions with CYP3A4 substrates and/or inducers is clinically significant.

The quantitative importance of CYP3A4 on the overall disposition of trazodone in man is not currently known, and such knowledge will depend upon the elucidation of the P450 enzymes involved in trazodone's other metabolic pathways. However, because approximately 20% of a dose of trazodone is recovered in urine as triazolopropionic acid and its conjugates, which is the other fragment formed when trazodone is *N*-dealkylated to mCPP (Haria *et al.*, 1994; Yamato *et al.*, 1974a, 1974b), it is reasonable to assume that 20% of the dose is also converted to mCPP. Furthermore, plasma levels of mCPP reach 1–20% those of the parent compound (Otani *et al.*, 1996; Vatassery *et al.*, 1997; Yasui *et al.*, 1995); therefore, CYP3A4 is expected to play a significant role in trazodone's metabolism.

The present experiments are a direct examination of trazodone metabolism to mCPP by the P450 enzymes and provide evidence that CYP3A4 is a major enzyme responsible for this biotransformation. This finding indicates that the potential for drug-drug interactions between trazodone and other substrates or inhibitors of CYP3A4 exists.

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Footnotes

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Abbreviations used are::

mCPP m-chlorophenylpiperazine
P450 cytochrome P450

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References

1. Aranow RR, Hudson JL, Harrison GP, Grady TA, Laane TA, Bell IR, Cole JO (1989) Elevated antidepressant levels after addition of fluoxetine. *Am J Psychiatry* **146**:911–913. » [Abstract/FREE Full Text](#)
2. Rainaldi RI, Friderici A, Giannannelli M, Palazzo G (1974) Basic metabolites of trazodone in humans. *Arzneimittelforschung* **24**:1699–1706. » [Medline](#)
3. Conn JP, Sanders-Bush E (1987) Relative efficacies of piperazines at the 5-hydroxytryptamine hydroxylase-linked serotonergic (5-HT₂ and 5-HT_{1C}) receptors. *J Pharmacol Exp Ther* **242**:552–557. » [Abstract/FREE Full Text](#)
4. Crews HK, Lennard MS, Tucker GT, Woods ER, Haddock RF (1992) The effect of selective serotonin reuptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Pharmacol* **34**:262–265.
5. Fahre I F (1990) Trazodone dosing regimen: Experience with single daily administration. *J Clin Psychiatry* **51**:23–26.
6. Fiorella D, Rahin RA, Winter JC (1995) The role of the 5-HT_{2A} and 5-HT_{2C} receptors in the stimulant effects of m-chlorophenylpiperazine. *Psychopharmacol* **119**:222–230. » [CrossRef](#) » [Medline](#)
7. Greenblatt DJ, von Moltke LL, Schmider JS, Harmatz JS, Shader PI (1996) Inhibition of human cytochrome P4503A isoforms by fluoxetine and norfluoxetine: *In vitro* and *in vivo* studies. *J Clin Pharmacol* **36**:792–798. » [Medline](#)
8. Guengerich FP (1996) *In vitro* techniques for studying drug metabolism. *J Pharmacokinetics Biopharm* **24**:521–533. » [CrossRef](#) » [Medline](#)
9. Haria M, Fitton A, McTavish D (1994) Trazodone: A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. *Drugs Aging* **4**:331–355. » [Medline](#)
10. Harvey AT, Breckon SH (1995) Interactions of serotonin reuptake inhibitors with tricyclic antidepressants (Letter). *Arch Gen Psychiatry* **52**:783–784. » [Abstract/FREE Full Text](#)
11. Ishida M, Otani K, Kaneko S, Ohkubo T, Otsuoi T, Yasui N, Mihara K, Hirauchi H, Sugawara K (1995) Effects of various factors on steady state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine. *Int Clin Psychopharmacol* **10**:143–146. » [Medline](#)
12. Iwatsubo T, Hirata N, Ogie T, Suzuki H, Shimada N, Oishi K, Ishizaki T, Green CE, Tveit CA, Sugiyama Y (1997) Prediction of *in vivo* drug metabolism in the human liver from *in vitro* metabolism data. *Pharmacol Ther* **73**:147–171. » [CrossRef](#) » [Medline](#)
13. Jacobson EM (1990) Low-dose trazodone as a hypnotic in patients treated with MAOIs and other psychotropics: A pilot study. *J Clin Psychiatry* **51**:298–302. » [Medline](#)
14. Kahn RS, Wetzler S (1991) m-Chlorophenylpiperazine as a probe of serotonin function. *Biol Psychiatry* **30**:1139–1166. » [CrossRef](#) » [Medline](#)
15. Mass M, Westenhoff H, Vandenlaanhe E, Demedts P, Waiters A, Neale H, Metzler HV (1997) Effects of trazodone and fluoxetine in the treatment of major depression: Therapeutic pharmacokinetic and pharmacodynamic interactions through formation of meta-chlorophenylpiperazine. *J Clin Psychopharmacol* **17**:358–364. » [CrossRef](#) » [Medline](#)
16. Melzack M, Raska I, Mai I (1979) 1-(m-Chlorophenyl)piperazine: A metabolite of trazodone isolated from rat urine. *J Pharm Pharmacol* **31**:855–856. » [Medline](#)
17. Metz A, Shader RI (1990) Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. *Int Clin Psychopharmacol* **5**:191–194. » [Medline](#)
18. Monteleone P, Gnani G, Delrio G (1989) Plasma trazodone concentrations and clinical response in elderly depressed patients: A preliminary study. *J Clin Psychopharmacol* **9**:284–287. » [Medline](#)

19. Nierenberg AA, Cole JO, Glass I (1992) Possible trazodone potentiation of fluoxetine: A case series. *J Clin Psychiatry* **53**:83–85. » [Medline](#)
20. Nierenberg AA, Adler LA, Paslow F, Zornberg G, Rosenthal M (1994) Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* **151**:1069–1072. » [Abstract/FREE Full Text](#)
21. Nilsen OG, Dale O, Husebo R (1993) Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* **72**:286–289. » [Medline](#)
22. Otani K, Ishida M, Kaneko S, Mihara K, Ohkuho T, Otsanai T, Sugawara K (1996) Effects of carbamazepine coadministration on plasma concentrations of trazodone and its active metabolite, m-chlorophenylpiperazine. *Ther Drug Monit* **18**:164–167. » [CrossRef](#) » [Medline](#)
23. Preskorn S (1996) *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors (Appendix)*. (Professional Communications, Inc. Cado, OK).
24. Schmider I, Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI (1996) Inhibition of cytochrome P450 by nefazodone in vitro: Studies of dextromethorphan O- and N-demethylation. *Br J Clin Pharmacol* **41**:339–343. » [CrossRef](#) » [Medline](#)
25. Vatassery GT, Holden LA, Hazel DK, Duviken MW (1997) Determination of trazodone and its metabolite, 1-m-chlorophenylpiperazine, in human plasma and red blood cell samples by HPLC. *Clin Biochem* **30**:149–153. » [CrossRef](#) » [Medline](#)
26. von Moltke LL, Greenblatt DJ, Harmatz JS, Duan SX, Harrel LM, Cottrill-Birba MM, Pritchard GA, Wright CF, Shader RI (1996) Triazolam biotransformation by human liver microsomes in vitro: Effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. *J Pharmacol Exp Ther* **276**:370–379. » [Abstract/FREE Full Text](#)
27. von Moltke LL, Greenblatt DJ, Schmider I, Harmatz JS, and Shader RI (1995) Metabolism of drugs by cytochrome P450 3A isoform: Implications for drug interactions in psychopharmacology. *Clin Pharmacokinet* **29**(Suppl. 1):33–44.
28. Wilkinson GR (1996) Cytochrome P450 3A (CYP3A) metabolism: Prediction of *in vivo* activity in humans. *J Pharmacokinet Biopharm* **24**:475–489. » [CrossRef](#) » [Medline](#)
29. Yamato C, Takahashi T, Fujita T (1974a) Studies on the metabolism of trazodone: I. Metabolic fate of [¹⁴C]trazodone hydrochloride in rats. *Xenobiotica* **4**:313–326. » [Medline](#)
30. Yamato C, Takahashi T, Fujita T, Kurivama S, Hirase N (1974b) Studies on the metabolism of trazodone: II. Metabolic fate after intravenous administration and effects on liver microsomal drug-metabolizing enzymes in rats. *Xenobiotica* **4**:765–777.
31. Yasui N, Otani K, Kaneko S, Ohkuho T, Otsanai T, Ishida M, Mihara K, Kondo T, Sugawara K, Fukushima Y (1995) Inhibition of trazodone metabolism by thioridazine in humans. *Ther Drug Monit* **17**:333–335. » [Medline](#)

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Drug Metab. Dispos. May 1, 2003 31:596-605

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