

# Selections from a literature search on the effects, mechanism of action, and metabolism of mCPP, the principal metabolite of Trazodone, with references.

Kevin Eric Saunders a/k/a bonze blayk (5/22/00)

## Effects of mCPP

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<http://www.vh.org/Providers/Conferences/CPS/04.html>

University of Iowa Health Care Clinical Psychopharmacology Seminar: Atypical Neuroleptics, Paul Perry, Ph.D, Brian C. Lund, Pharm.D. Peer Review Status: Internally Peer Reviewed

"It is well known that central serotonin agonists such as LSD and MCPP as well as dopamine agonists such as amphetamine and cocaine are capable of producing psychotic reaction (Huttunen 1995)."

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Int Clin Psychopharmacol 1998 Sep;13(5):225-8

Occurrence of trazodone-induced delirium.

Lennkh C, Fischer P, Kufferle B, Kasper S

Department of General Psychiatry, University Hospital of Psychiatry, Vienna, Austria.

Trazodone, a triazolepyridine derivate, is both chemically and pharmacologically distinct from other serotonin reuptake inhibitors and possesses antidepressant, anxiolytic and hypnotic activity. We observed trazodone-induced delirium in three depressed patients who also suffered from preexisting organic cerebral lesions (two cases) or thyroideal dysfunction (one case). The appearance of hallucinations, psychomotoric agitation, and cognitive changes after initiation of trazodone therapy and their prompt cessation after drug discontinuation led to the impression that these were drug-induced phenomena. One possible hypothesis for the observed deliria is an oversensitivity to the effect of meta-chlorphenylpiperazine [mCPP], which is a metabolite of trazodone with specific 5-HT agonistic properties.

PMID: 9817628, UI: 99032566

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>>> mCPP is an anorectic agent. (2 mg/kg)

>>> "trazodone may have specific antipanic and antiphobic actions" [but the case is much different for its metabolite mCPP...]

>>> "Challenge with m-CPP induced depersonalization significantly more than did placebo."

>>> "...it is doubtful whether mCPP is a useful compound for challenge tests in view of the large pharmacokinetic variability after intravenous and oral administration. The effects of mCPP are consistent with disinhibition of the central nervous system." (0.5 mg/kg oral)

>>> "infusion of mCPP caused significant increases in self-ratings for the psychological and physical symptoms of anxiety, for the symptoms of panic attack, and in the plasma levels of cortisol and prolactin, with four subjects (33%) experiencing an mCPP-induced 'panic attack.'" (0.08 mg/kg i.v. over 2 min)

>>> "administration of m-CPP was associated with significant behavioral effects, particularly self-rated measures of anxiety, altered self-reality, functional deficit and OCD symptoms." (0.08 mg/kg i.v.)

>>> "These results suggest that mCPP (and TMPP) are anxiogenic but not sedative in these tests." (0.1-1.0 mg/kg)

>>> "MCPP had anxiogenic effects in both the healthy subjects and patients"

>>> "...a significant correlation was found across all subjects between clinical anxiety level and cortisol release on MCPP." (0.25 mg/kg oral)

>>> "...the atypical AD trazodone, enhanced freezing behavior, suggesting anxiogenic-like behavior."

>>> mCPP in small doses (0.5 mg/kg oral) leads to significant increases in euphoria and anxiety.

### **Mechanism of action of mCPP**

>>> "After a single oral dose and after multiple ip or po administration of TRZ [Trazodone], the brain level of CPP [mCPP] exceeded markedly that of the parent compound."

>>> "mCPP and MK 212 selectively inhibit mesolimbic dopaminergic function by acting on 5-HT<sub>2C</sub> receptors"

>>> "The present data suggest that mCPP elicits a compound stimulus which is mediated by agonist interactions at the 5-HT<sub>2C</sub> receptor and possibly additional interactions with 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, and/or 5-HT<sub>1B</sub> receptors."

>>> "DOI and mCPP, but not 6-chloro-2-[1-piperazinyl]-pyrazine, elicited a dose-dependent head-twitch response (HTR)."

>>> "992 and trazodone attenuated 5-HT<sub>2A/2C</sub> receptor agonist-induced head-twitches in mice, indicating that these drugs had 5-HT<sub>2A</sub> receptor antagonistic activity."

>>> "The present results suggest that the discriminative stimulus effects of mCPP in rats are mediated primarily by postsynaptic 5-HT<sub>2C</sub> receptors."

>>> "DOI is an hallucinogen having high affinity and selectivity as an agonist at 5-HT<sub>2A/2C</sub> receptors [like mCPP].... [fluoxetine was among compounds which] had either inconsistent or no effect on the DOI-induced behaviors... . The data show that antipsychotic agents, as a drug class, effectively block the effects of DOI. "

>>> "Although it has not yet been demonstrated that mCPP and TMPP are agonists at central 5-HT<sub>2A</sub> receptors, this possibility should be considered when evaluating in vivo effects of these drugs."

>>> "The principle of the SDAs [antipsychotics] is that the drug should be a potent serotonin 5-HT<sub>2A</sub> antagonist, with slightly less potent dopamine D<sub>2</sub> receptor-blocking properties."

>>> "mCPP had a relative efficacy of 65% at 5-HT<sub>2C</sub> receptors but <25% at either 5-HT<sub>2A</sub> or 5-HT<sub>2B</sub> receptors."

### Metabolism of mCPP

>>> "These results confirm that CYP2D6 is the isoform responsible for the p-hydroxylation of mCPP, and indicate that caution should be exercised in coprescribing inhibitors or substrates of CYP2D6 with drugs that have mCPP as a metabolite."

>>> "The present results indicate 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."

>>> "clearance of mCPP is mediated by P450-2D6"

>>> "A large number of drugs (including beta blockers, antiarrhythmics, tricyclic antidepressants, and neuroleptics) are substrates for CYP2D6, and a 10- to 20-fold difference in metabolism of some of these drugs accounts for the interest in this polymorphism"

>>> "The present study thus suggests that the CYP2D6 genotype cannot predict the C<sub>ss</sub> of these compounds [trazodone and mCPP]."

>>> "Smokers had significantly ( $p < 0.05$ ) lower plasma concentrations of trazodone and higher mCPP/trazodone ratios than non-smokers."

# References from a literature search on the effects, mechanism of action, and metabolism of mCPP, the principal metabolite of Trazodone

## Effects of mCPP

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>>> mCPP is an anorectic agent. (2 mg/kg)

Abstract Volume 137 Issue 1 (1998) pp 43-49

original investigation: Serotonin receptors in the caudal brainstem are necessary and sufficient for the anorectic effect of peripherally administered mCPP

J. M. Kaplan, Sarah Song, Harvey J. Grill

University of Pennsylvania, 3815 Walnut Street, Philadelphia, PA 19104, USA

Received: 24 June 1997 / Final version: 13 November 1997

Abstract The role of caudal brainstem 5-HT receptors in mediating the anorectic effect of the direct 5-HT<sub>2C/1B</sub> agonist, mCPP [1-(3-chlorophenyl)piperazine dihydrochloride], was evaluated. We demonstrated, first, that systemic injections of mCPP yielded a dose-related suppression of intra-oral intake of 12.5% glucose in intact rats and in chronically maintained supracollicular decerebrate rats. The results of the decerebrate experiment suggest that 5-HT receptors in the caudal brainstem are sufficient for mediating the drug's intake effect. We also showed a dose-related intake suppression when mCPP was delivered to the fourth ventricle of intact rats, with potent suppression obtained at doses well below threshold for systemic administration. Whether and to what extent the 5-HT<sub>2C/2A</sub> antagonist, mesulergine reverses the intake suppression that follows systemic or 4th ICV injection of mCPP was examined. Fourth ICV co-administration of mesulergine (60 µg) and mCPP (40 µg) eliminated the approximately 50% intake suppression observed when mCPP was delivered alone, a result that affirms the receptor selectivity of the 4th ICV agonist effect. We showed, further, that 4th ICV mesulergine (60 µg) completely reversed the intake suppression produced by systemic mCPP (2 mg/kg). The latter result indicates that stimulation of 5-HT receptors in the caudal brainstem is necessary for the intake suppression produced by systemic administration of this 5-HT agonist in the intact rat.

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>>> "trazodone may have specific antipanic and antiphobic actions" [but the case is much different for its metabolite mCPP...]

Am J Psychiatry 1987 Jun;144(6):785-7

Trazodone in the treatment of panic disorder and agoraphobia with panic attacks.

Mavissakalian M, Perel J, Bowler K, Dealy R

Eleven patients with panic disorder or agoraphobia with panic attacks completed an 8-week single-blind trial of trazodone (300 mg/day) without concurrent behavioral instructions. The measures of change included ratings of generalized and panic anxiety, phobias, and depression and a behavioral avoidance test, which were administered during a baseline period of placebo administration and at 4 and 8 weeks of the trial. There was significant improvement on all symptom dimensions, which suggests that trazodone may have specific antipanic and antiphobic actions and underscores the importance of serotonergic mechanisms in these anxiety disorders.

Publication Types: Clinical trial

PMID: 3296792, UI: 87239026

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>>> "Challenge with m-CPP induced depersonalization significantly more than did placebo."

Psychiatry Res 1995 Sep 29;58(2):161-4

Induction of depersonalization by the serotonin agonist meta-chlorophenylpiperazine.

Simeon D, Hollander E, Stein DJ, DeCaria C, Cohen LJ, Saoud JB, Islam N, Hwang M

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029-6574, USA.

Sixty-seven subjects, including normal volunteers and patients with obsessive-compulsive disorder, social phobia, and borderline personality disorder, received ratings of depersonalization after double-blind, placebo-controlled challenges with the partial serotonin agonist meta-chlorophenylpiperazine (m-CPP). Challenge with m-CPP induced depersonalization significantly more than did placebo. Subjects who became depersonalized did not differ in age, sex, or diagnosis from those who did not experience depersonalization. There was a significant correlation between the induction of depersonalization and increase in panic, but not nervousness, anxiety, sadness, depression, or drowsiness. This report suggests that serotonergic dysregulation may in part underlie depersonalization.

Publication Types: Clinical trial Randomized controlled trial

PMID: 8570768, UI: 96124215

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>>> "...it is doubtful whether mCPP is a useful compound for challenge tests in view of the large pharmacokinetic variability after intravenous and oral administration. The effects of mCPP are consistent with disinhibition of the central nervous system." (0.5 mg/kg oral)

J Clin Psychopharmacol 1998 Aug;18(4):289-95

Pharmacokinetic and pharmacodynamic profile of oral and intravenous meta-chlorophenylpiperazine in healthy volunteers.

Gijsman HJ, Van Gerven JM, Tieleman MC, Schoemaker RC, Pieters MS, Ferrari MD, Cohen AF, Van Kempen GM

Department of Psychiatry, Centre for Human Drug Research, Leiden University Medical Centre, The Netherlands.

meta-Chlorophenylpiperazine (mCPP) is a compound that is frequently used in challenge tests of the serotonergic system. Its human pharmacology is largely unexplored. The objective of this study was to investigate the pharmacokinetic and pharmacodynamic profile of mCPP. Eight female and six male healthy volunteers were included in a randomized, double-blind, double-dummy, three-way crossover design of single-dose intravenous (0.1 mg/kg), oral (0.5 mg/kg), and placebo treatment, with 24-hour follow-up. mCPP showed a large variability in clearance (11-92 mL/hr) and bioavailability (14-108%). Two female subjects dropped out because of headache and dysphoria. During the 27 occasions in which mCPP was administered, autonomic physical symptoms were observed in 23 subjects and disturbances of mood in 6 subjects. Oral and intravenous mCPP caused sudden increases in cortisol levels, prolactin levels, and total scores of the Body Sensation Questionnaire. Administration of mCPP also led to concentration-dependent increases of saccadic peak velocity and adaptive tracking performance and to a decrease of electroencephalographic occipital theta activity. No clinically relevant effects on electrocardiogram, temperature, and blood pressure were found. In conclusion, it is doubtful whether mCPP is a useful compound for challenge tests in view of the large pharmacokinetic variability after intravenous and oral administration. The effects of mCPP are consistent with disinhibition of the central nervous system.

Publication Types: Clinical trial Randomized controlled trial

PMID: 9690694, UI: 98353004

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>>> "infusion of mCPP caused significant increases in self-ratings for the psychological and physical symptoms of anxiety, for the symptoms of panic attack, and in the plasma levels of cortisol and prolactin, with four subjects (33%) experiencing an mCPP-induced 'panic attack.'" (0.08 mg/kg i.v. over 2 min)

Biol Psychiatry 1994 Sep 1;36(5):309-16

The 5-HT<sub>3</sub> antagonist, BRL 46470 does not attenuate m-chlorophenylpiperazine (mCPP)-induced changes in human volunteers.

Silverstone PH, Cowen PJ

MRC Unit of Clinical Pharmacology, Littlemore Hospital, Oxford, U.K.

Results from animal studies have suggested that serotonin (5-HT) antagonists acting on the 5-HT<sub>3</sub> receptor may have anxiolytic properties. We have assessed whether pretreatment with the 5-HT<sub>3</sub> receptor antagonist BRL 46470 (1 mg orally) attenuates the increase in anxiety induced in healthy volunteers by intravenous infusion of m-chlorophenylpiperazine (mCPP: 0.08 mg/kg over 2 min). In this double-blind placebo-controlled crossover study in 12 healthy men who were volunteers, infusion of mCPP caused significant increases in self-ratings for the psychological and physical symptoms of anxiety, for the symptoms of panic attack, and in the plasma levels of cortisol and prolactin, with four subjects (33%) experiencing an mCPP-induced "panic attack." Pretreatment with BRL 46470 did not attenuate any of these mCPP-induced changes. These results do not support suggestions from animal studies that 5-HT<sub>3</sub> receptor antagonists can attenuate mCPP-induced anxiety, although it is conceivable that a different dose of BRL 46470 may have been effective.

Publication Types: Clinical trial Randomized controlled trial

PMID: 7993957, UI: 95086129

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>>> "administration of m-CPP was associated with significant behavioral effects, particularly self-rated measures of anxiety, altered self-reality, functional deficit and OCD symptoms." (0.08 mg/kg i.v.)

Psychiatry Res 1998 Jun 2;79(1):11-20

Acute intravenous administration of ondansetron and m-CPP, alone and in combination, in patients with obsessive-compulsive disorder (OCD): behavioral and biological results.

Broocks A, Pigott TA, Hill JL, Canter S, Grady TA, L'Heureux F, Murphy DL

Section on Clinical Neuropharmacology, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD, USA.

Obsessive-compulsive disorder (OCD) has been linked to abnormal function of brain serotonin (5-HT) pathways. Since ondansetron is a highly selective 5-HT<sub>3</sub> receptor antagonist, the present study was undertaken to investigate 5-HT<sub>3</sub> function in OCD. We administered m-CPP (0.08 mg/kg i.v.) and the potent 5-HT<sub>3</sub> antagonist, ondansetron (0.15 mg/kg i.v.), to 11 OCD patients. All of the subjects received four separate challenges (m-CPP + placebo, m-CPP + ondansetron, ondansetron + placebo and placebo + placebo). In comparison to placebo, administration of m-CPP was associated with significant behavioral effects, particularly self-rated measures of anxiety, altered self-reality, functional deficit and OCD symptoms. Pretreatment with ondansetron did not affect any of the self-rated behavioral symptoms. After administration of m-CPP relative to placebo, significant increases in plasma cortisol and prolactin were

found. These changes were not affected by ondansetron. In conclusion, our results do not support the hypotheses that 5-HT<sub>3</sub> receptor-mediated mechanisms modulate m-CPP's behavioral and neuroendocrine effects in patients with OCD.

Publication Types: Clinical trial Randomized controlled trial

PMID: 9676822, UI: 98339444

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>>> "These results suggest that mCPP (and FMPP) are anxiogenic but not sedative in these tests." (0.1-1.0 mg/kg)

Eur J Pharmacol 1989 May 30;164(3):445-54

Anxiogenic-like effects of mCPP and FMPP in animal models are opposed by 5-HT<sub>1C</sub> receptor antagonists.

Kennett GA, Whitton P, Shah K, Curzon G

Department of Neurochemistry, Institute of Neurology, London, U.K.

1-(3-chlorophenyl)piperazine (mCPP) and 1-[3-(trifluoromethyl)phenyl]piperazine (FMPP) (0.1-1.0 mg/kg) reduce total interaction time in a rat social interaction test under low light familiar conditions and its following components; grooming, following, crawling over, fighting, sniffing. Locomotion was only reduced by the highest dose of mCPP. mCPP also reduced activity in the light but not total locomotion in a light/dark transition test. These results suggest that mCPP (and FMPP) are anxiogenic but not sedative in these tests. The effect of mCPP on social interaction was blocked by three antagonists which share a high affinity for 5-HT<sub>1C</sub> and 5-HT<sub>2</sub> receptors: mianserin, cyproheptadine and metergoline but not by the 5-HT<sub>2</sub> antagonists ketanserin or ritanserin or the 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> antagonists cyanopindolol and (-)-propranolol. It was prevented by a low (0.05 mg/kg) but not by a high (1.0 mg/kg) dose of ICS 205,930 a specific 5-HT<sub>3</sub> antagonist reported to be anxiolytic at low doses. It was also prevented by chronic pretreatment with the anxiolytic drug chlordiazepoxide. These results argue for an anxiogenic action of mCPP mediated by 5-HT<sub>1C</sub> receptors. Since the chronic chlordiazepoxide pretreatment did not prevent the hypolocomotion or hypophagia induced by mCPP at high dosage (5 mg/kg) these latter effects are unlikely to be secondary to anxiety.

PMID: 2767117, UI: 89356809

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>>> "MCPD had anxiogenic effects in both the healthy subjects and patients"

Psychopharmacology (Berl) 1987;92(1):14-24

Serotonin function in anxiety. II. Effects of the serotonin agonist MCPD in panic disorder patients and healthy subjects.

Charney DS, Woods SW, Goodman WK, Heninger GR

To assess the role of serotonin function in the development of panic anxiety, the behavioral and biochemical responses to the serotonin receptor agonist, m-chlorophenylpiperazine (MCPD) was examined in healthy subjects and agoraphobic and panic disorder patients. MCPD had anxiogenic effects in both the healthy subjects and patients. Panic attacks meeting DSM-III criteria occurred following MCPD in 12 of 23 patients and 6 of 19 healthy subjects (NS) and other ratings of anxiety also did not distinguish the two groups. MCPD resulted in significant but similar increases in cortisol, prolactin, and growth hormone in the healthy subjects and patients. The results of this investigation suggest that serotonin neuronal dysfunction may not be of etiologic significance in most panic disorder patients. However, the observed anxiogenic properties of MCPD suggest that additional studies of the role of serotonin systems in the pathophysiology of human anxiety disorders are indicated.

PMID: 3110824, UI: 87261630

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>>> "...a significant correlation was found across all subjects between clinical anxiety level and cortisol release on MCPP." (0.25 mg/kg oral)

Psychopharmacology (Berl) 1988;96(3):360-4

Neuroendocrine evidence for serotonin receptor hypersensitivity in panic disorder.

Kahn RS, Asnis GM, Wetzler S, van Praag HM

Department of Psychiatry, Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY 10467.

Normal controls (NC) (n = 15), patients with panic disorder (PD) (n = 13) and patients with major depression (MD) (n = 17) were challenged with a single, oral dose (0.25 mg/kg) of the selective 5HT agonist m-chlorophenyl-piperazine (MCPP) or placebo. Blood samples were assayed for cortisol and MCPP levels every 30 min. The PD group had an augmented cortisol release when compared to the other two groups. Finally, a significant correlation was found across all subjects between clinical anxiety level and cortisol release on MCPP. These data support the hypothesis of 5HT receptor hypersensitivity in PD.

Publication Types: Clinical trial Controlled clinical trial

PMID: 2906153, UI: 89129248

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Biol Psychiatry 1990 Dec 15;28(12):1053-7

Hypersensitivity to m-chlorophenylpiperazine in a subject with subclinical panic attacks.

Kalus O, Kahn RS, Wetzler S, Asnis GM, van Praag HM

Albert Einstein College of Medicine, Bronx, NY.

PMID: 2288999, UI: 91145509

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Psychopharmacology (Berl) 1990;100(3):339-44

Effects of m-chlorophenylpiperazine in normal subjects: a dose-response study.

Kahn RS, Wetzler S, Asnis GM, Kling MA, Suckow RF, van Praag HM

Department of Psychiatry, Albert Einstein College of Medicine, Montefiore Medical Center, New York, NY 10467.

m-Chlorophenylpiperazine (MCPP), a direct 5HT receptor agonist, was administered orally to 20 normal subjects in two doses (0.25 and 0.5 mg/kg) in a placebo-controlled design. Behavioral responses; ACTH, cortisol, prolactin and MCPP blood level; temperature and pulse rate were measured over a 210-min period after administration of tablets. Non-linear dose-response relationships between MCPP and ACTH, cortisol and prolactin response were found. On the higher dose, a significant increase in the number of physical symptoms was also noted and three subjects (15%) had a panic attack, while one subject (5%) had a panic attack on the lower dose. No effects on other behavioral variables, pulse rate and temperature were found using either dose. These findings attest to the usefulness of MCPP as a challenge agent to assess 5HT receptor hypersensitivity when given at a low oral dose (i.e. around 0.25 mg/kg), and to assess 5HT receptor hyposensitivity when given at higher oral doses (i.e. around 0.5 mg/kg).



PMID: 2156278, UI: 90193016

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Psychopharmacology (Berl) 1989;98(2):275-82

Comparative anxiogenic, neuroendocrine, and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers.

Murphy DL, Mueller EA, Hill JL, Tolliver TJ, Jacobsen FM

Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD 20892.

The serotonin agonist m-chlorophenylpiperazine (m-CPP) had greater anxiogenic and other mood and cognitive effects when administered intravenously (0.1 mg/kg) rather than orally (0.5 mg/kg) to healthy subjects. Nonetheless, similar elevations in peak plasma cortisol and prolactin concentrations were obtained with the two dosage regimens, and temperature elevations were greater after oral m-CPP. Plateau phase plasma concentrations of m-CPP at the times of the maximum neuroendocrine responses to intravenous and oral m-CPP were similar. Since all rodent and nonhuman primate studies have used parenterally administered m-CPP, and previous clinical investigations using intravenous rather than oral m-CPP have yielded somewhat discrepant results, our normative data should be useful for comparing results across different human studies and across species.

Publication Types: Clinical trial Controlled clinical trial

PMID: 2502799, UI: 89331779

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>>> "...the atypical AD trazodone, enhanced freezing behavior, suggesting anxiogenic-like behavior."

Pharmacol Biochem Behav 2000 Feb;65(2):339-44 Related Articles, Books

Anxiolytic-like effects of antidepressants after acute administration in a four-plate test in mice.

Hascoet M, Bourin M, Colombel MC, Fiocco AJ, Baker GB

Faculty of Medicine and GIS Medicament, Neurobiologie de l'anxiete Faculte de Medecine, Nantes, France.

The four-plate test (FPT) is an animal model of anxiety based on stress caused by unconditioned fear. An increase of spontaneous punished behavior was used as a measure to determine the anxiolytic effects of various antidepressants (ADs). In the present study, ADs with different mechanisms of action, including tricyclics, selective serotonin reuptake inhibitors (SSRIs), a monoamine oxidase inhibitor (MAOI), and atypicals, were studied in the FPT to evaluate their anxiolytic-like effects following acute administration. The number of punished crossings was dramatically increased by the SSRIs citalopram, fluvoxamine, and paroxetine, but not fluoxetine. The mixed 5-HT/NE reuptake inhibitors, milnacipran and venlafaxine, also demonstrated strong antipunishment effects. The specific NE reuptake inhibitors, desipramine and maprotiline, and the atypical AD trazodone, enhanced freezing behavior, suggesting anxiogenic-like behavior. It was concluded that, in the FPT, a model based on spontaneous response, where animals are exposed to an aversive environment from which they can only escape by being motionless, this kind of behavior might be related to anticipatory anxiety. In this situation, ADs acting preferentially on 5-HT transmission possessed clear anxiolytic like effects. The balance between the two transmitters, 5-HT and NE, seemed to be a crucial factor.

PMID: 10672988, UI: 20135543

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Int Clin Psychopharmacol 1994 Sep;9(3):173-8 Related Articles, Books

The effects of administration of mCPP on psychological, cognitive, cardiovascular, hormonal and MHPG measurements in human volunteers.

Silverstone PH, Rue JE, Franklin M, Hallis K, Camplin G, Laver D, Cowen PJ

MRC Unit of Clinical Pharmacology, Littlemore Hospital, Oxford, UK.

m-Chlorophenylpiperazine (mCPP) is a metabolite of the antidepressant trazodone which has been widely used in psychopharmacology research as a probe of serotonin (5-hydroxytryptamine; 5-HT) function. However, in addition to binding at 5-HT receptors it also binds strongly to alpha 2-adrenoceptors, and it is conceivable that some of the physical and psychological symptoms previously reported following mCPP infusion are due to effects upon central noradrenergic neurotransmitter function. In this double-blind placebo-controlled balanced-crossover study in 12 healthy male volunteers we have examined the effects of infusion of mCPP (0.08 mg/kg over 2 min) on symptoms of anxiety, cognitive performance, pulse and blood pressure, and plasma concentrations of adrenocorticotrophic hormone (ACTH), cortisol, prolactin, growth hormone, and the noradrenaline metabolite 3-methoxy-4-hydroxyphenyl glycerol (MHPG). The results confirm previous findings that in humans mCPP causes significant increases in the symptoms of anxiety, and in the plasma concentrations of cortisol, prolactin and growth hormone. In addition, our results demonstrate that mCPP causes no significant changes in cognitive performance, in pulse or systolic blood pressure, or in the plasma concentration of MHPG. Since pulse, systolic blood pressure and MHPG plasma concentrations all to some degree reflect central noradrenergic activity, we believe it unlikely that the psychological and hormonal effects of mCPP are due primarily to effects on noradrenergic neurotransmission. Further studies to address this specific issue are needed, however, before firm conclusions can be reached.

Publication Types: Clinical trial Randomized controlled trial

PMID: 7814826, UI: 95114336

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J Clin Psychiatry 1991 Jul;52(7):294-9

Fluoxetine versus trazodone: efficacy and activating-sedating effects.

Beasley CM Jr, Dornseif BE, Pultz JA, Bosomworth JC, Saylor ME

Division of Clinical Neurosciences, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind. 46285.

**BACKGROUND:** The efficacy and safety of fluoxetine (N = 65; median sustained dose, 20 mg/day) and of trazodone (N = 61; median sustained dose, 250 mg/day) were compared in a trial in outpatients with major depressive episode. The incidence and temporal patterns of activation and sedation were also assessed. **METHOD:** Men and women who met DSM-III criteria for nonpsychotic major depressive episode (but with a current episode greater than or equal to 4 weeks) and had a 21-item Hamilton Rating Scale for Depression (HAM-D21) score greater than 20 were selected. After single-blind placebo was administered for 1 week, eligible patients were randomized to double-blind fluoxetine or trazodone treatment for up to 6 weeks. Efficacy (HAM-D21, Clinical Global Impressions Scales for Severity and Improvement, Patient Global Impressions Scale for Improvement, Guild Memory Test) and adverse events were evaluated weekly. **RESULTS:** The HAM-D21 score improved within both treatment groups (p less than .001). The groups were similar with respect to endpoint mean HAM-D21 improvement. For individual adverse events that developed or worsened during therapy, more fluoxetine-treated patients reported rhinitis and tremor (p less than or equal to .05), while more trazodone-treated patients reported somnolence and dizziness (p less than or equal to .05). More combined events suggesting activation (agitation, anxiety, nervousness, insomnia) were reported with fluoxetine than with trazodone (15.4% vs. 3.3%, p less than or equal to .05), while more combined events suggesting sedation (somnolence, asthenia) were reported with trazodone than with fluoxetine (42.6% vs. 21.5%, p less than or equal to .05). Discontinuation rates for activation and sedation did not differ between treatments. Numerically, more sedation (21.5%) than activation (15.4%) was reported with fluoxetine. **CONCLUSIONS:** There was little clinical difference between treatments with regard to efficacy and safety. The occurrence and

temporal patterns of activation and sedation differed within and between treatments.

Publication Types: Clinical trial Multicenter study Randomized controlled trial

PMID: 2071559, UI: 91302273

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Boll Chim Farm 1990 May;129(5):183-9 Related Articles, Books

In-vivo metabolism of 4-substituted arylpiperazines to pharmacologically active 1-aryl piperazines.

Caccia S

Laboratory of Drug Metabolism, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

A common metabolic process of 4-substituted arylpiperazine pharmacological agents is cleavage of the side-chain to yield 1-aryl piperazines. These metabolites are a well-known class of centrally active compounds and their formation may therefore be a pharmacologically significant pathway, at least in certain species, for derivatives that undergo extensive cleavage of the arylpiperazine side-chain. Of pharmacological relevance is the observation that they may have a spectrum of pharmacological actions different from the parent compound(s). As illustrated by the anxiolytic agent buspirone, its derivatives gepirone and isapirone and their common metabolite 1-(2-pyrimidinyl)-piperazine (PmP), parents drug(s) and metabolite may have quite different mechanism of action. In other cases, the 1-aryl piperazine metabolite and its parent drug(s) may act antagonistically (i.e. 1-(m-chlorophenyl)-piperazine, mCIPP, and its parent drugs trazodone and etoperidone). The kinetic properties of 1-aryl piperazine metabolites may differ from those of the parent compound, particularly in relation to the extent to which they enter the brain, the site of action of most of these compounds. The examples given although limited, provide evidence that kinetics and pharmacological studies on 1-aryl piperazine metabolites are important in seeking to understand the mechanism of action of the 4-substituted derivatives and in extrapolating pharmacological finding from animals to man.

Publication Types: Review Review, tutorial

PMID: 1982054, UI: 91190318

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>>> mCPP in small doses (0.5 mg/kg oral) leads to significant increases in euphoria and anxiety.

Clin Endocrinol Metab 1985 Dec;61(6):1179-84 Related Articles, Books

Neuroendocrine effects of M-chlorophenylpiperazine, a serotonin agonist, in humans.

Mueller EA, Murphy DL, Sunderland T

M-Chlorophenylpiperazine (m-CPP) produces effects on the central serotonergic system in animals compatible with direct agonist activity on postsynaptic serotonin receptors. Although it is a metabolite of the antidepressant trazodone, m-CPP has not previously been given to humans. To evaluate the neuroendocrine, behavioral, and physiological effects of m-CPP, 15 normal subjects were given 0.5 mg/kg m-CPP, orally. Administered acutely under double blind, placebo-controlled conditions, m-CPP was well tolerated by 14 of the 15 subjects; it produced significant increases in plasma PRL and cortisol and in body temperature, without changing pulse or blood pressure. The mean (SD) maximal increases over baseline for PRL, cortisol and temperature were 13.4 (9.9) ng/ml, 10.1 (6.7) micrograms/100 ml, and 0.4 (0.2) C, respectively. A small but significant increase in self-rated activation-euphoria and anxiety was noted by some subjects, whereas there were no significant effects on ratings of depression, dysphoria, altered self-reality, or functional impairment. These results are similar to those for other serotonin agonists and, thus, suggest that m-CPP merits further study as a pharmacological probe of serotonergic responsivity in humans. The results also support the hypothesis that serotonin plays a role in the regulation of PRL,

cortisol, body temperature, and mood.

Publication Types: Clinical trial Controlled clinical trial

PMID: 4055985, UI: 86034442

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Int Clin Psychopharmacol 1994 Sep;9(3):173-8

The effects of administration of mCPP on psychological, cognitive, cardiovascular, hormonal and MHPG measurements in human volunteers.

Silverstone PH, Rue JE, Franklin M, Hallis K, Camplin G, Laver D, Cowen PJ

MRC Unit of Clinical Pharmacology, Littlemore Hospital, Oxford, UK.

m-Chlorophenylpiperazine (mCPP) is a metabolite of the antidepressant trazodone which has been widely used in psychopharmacology research as a probe of serotonin (5-hydroxytryptamine; 5-HT) function. However, in addition to binding at 5-HT receptors it also binds strongly to alpha 2-adrenoceptors, and it is conceivable that some of the physical and psychological symptoms previously reported following mCPP infusion are due to effects upon central noradrenergic neurotransmitter function. In this double-blind placebo-controlled balanced-crossover study in 12 healthy male volunteers we have examined the effects of infusion of mCPP (0.08 mg/kg over 2 min) on symptoms of anxiety, cognitive performance, pulse and blood pressure, and plasma concentrations of adrenocorticotrophic hormone (ACTH), cortisol, prolactin, growth hormone, and the noradrenaline metabolite 3-methoxy-4-hydroxyphenyl glycerol (MHPG). The results confirm previous findings that in humans mCPP causes significant increases in the symptoms of anxiety, and in the plasma concentrations of cortisol, prolactin and growth hormone. In addition, our results demonstrate that mCPP causes no significant changes in cognitive performance, in pulse or systolic blood pressure, or in the plasma concentration of MHPG. Since pulse, systolic blood pressure and MHPG plasma concentrations all to some degree reflect central noradrenergic activity, we believe it unlikely that the psychological and hormonal effects of mCPP are due primarily to effects on noradrenergic neurotransmission. Further studies to address this specific issue are needed, however, before firm conclusions can be reached.

Publication Types: Clinical trial Randomized controlled trial

PMID: 7814826, UI: 95114336

## Mechanism of action of mCPP

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Neuropharmacology 1985 Nov;24(11):1067-71

Trazodone and m-chlorophenylpiperazine. Concentration in brain and receptor activity in regions in the brain associated with anxiety.

Smith TM, Suckow RF

Trazodone, its active metabolite 1-(m-chlorophenyl)piperazine (mCPP) and two isomers of mCPP were tested for affinity to the binding sites for [3H]flunitrazepam ([3H]FLU) and [3H]p-aminoclonidine ([3H]pAC) in the frontal cortex, amygdala and hippocampus of the rat. When tested at the binding site for [3H]flunitrazepam, trazodone showed an average IC50 of 1.7 mM in all three regions of the brain while mCPP yielded an average IC50 of 0.36 mM. These same two compounds, when tested at the binding site for [3H]p-aminoclonidine, resulted in an average IC50 of 4.5 microM for trazodone and 0.6 microM for mCPP. When plasma values of trazodone and mCPP in the rat were similar to those obtained in patients given therapeutic doses, the concentrations of trazodone were found to be between 6 and 7 microM and between 2 and 3 microM for mCPP in the same brain regions of the brain used in the binding assays. Thus, a sufficient concentration of trazodone and mCPP can accumulate in brain tissue to displace approx. 50% of the [3H]p-aminoclonidine from its binding site but very little [3H]flunitrazepam from its binding site. These results, combined with the reported anxiolytic effects of the alpha-2 agonist, clonidine and the noradrenergic hyperactivity theory of anxiety, indicate that the mechanism of the anxiolytic activity of trazodone, may be a direct action on the central alpha-2 binding site.

PMID: 4080105, UI: 86092543

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>>> "After a single oral dose and after multiple ip or po administration of TRZ [Trazodone], the brain level of CPP [mCPP] exceeded markedly that of the parent compound."

Pol J Pharmacol Pharm 1983 May-Jun;35(3):241-7

Effect of dosage and route of administration of trazodone on cerebral concentration of 1-m-chlorophenylpiperazine in rats. Kinetics of trazodone biotransformation in rats.

Rurak A, Melzacka M

The levels of trazodone (TRZ) and its metabolite, 1-m-chlorophenylpiperazine (CPP) in the rat brain were tested after single and multiple administration of TRZ ip or po. After a single oral dose and after multiple ip or po administration of TRZ, the brain level of CPP exceeded markedly that of the parent compound. Some of pharmacokinetic parameters of TRZ and CPP were significantly changed after chronic treatment. As the biological effect of CPP is opposite to that of its parent compound, the high level of metabolite in the central nervous system may affect strongly the pharmacological activity of TRZ.

PMID: 6622303, UI: 84015729

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>>> "mCPP and MK 212 selectively inhibit mesolimbic dopaminergic function by acting on 5-HT(2C) receptors"

Synapse 2000 Jan;35(1):53-61

Preferential modulation of mesolimbic vs. nigrostriatal dopaminergic function by serotonin(2C/2B) receptor agonists: a combined in vivo electrophysiological and microdialysis study.

Di Giovanni G, Di Matteo V, Di Mascio M, Esposito E

Istituto di Ricerche Farmacologiche "Mario Negri," Consorzio "Mario Negri" Sud, Santa Maria Imbaro (Chieti), Italy.

Electrophysiological and in vivo microdialysis were used to investigate and compare the effect of tonic activation of serotonin(2C/2B) (5-HT(2C/2B)) receptors on nigrostriatal and mesolimbic dopaminergic (DA) function. Thus, extracellular single unit recordings of neurochemically-identified DA neurons in the SNc and the VTA, as well as simultaneous monitoring of striatal and accumbal DA release were performed following the administration of the unselective 5-HT(2C/2B) agonists, mCPP (m-chlorophenylpiperazine) and MK 212 [6-chloro-2-(1-piperazinyl)piperazine]. Both mCPP (5-320 microg/kg i. v.) and MK 212 (5-320 microg/kg i.v.) dose-dependently decreased the firing rate of VTA DA neurons. The maximal effect was reached at the cumulative dose of 320 microg/kg mCPP and MK 212, which caused a decrease of 42.6 +/- 12.8% and 56.4 +/- 12.6%, respectively. In addition, the total number of events in bursts and the number of bursts of VTA DA cells were significantly reduced by both mCPP and MK 212. On the other hand, mCPP (5-320 microg/kg i.v.) and MK 212 (5-320 microg/kg i.v.) induced a slight decrease in the basal firing rate, but not in bursting activity of SNc DA neurons. Consistent with electrophysiological data, dialysate DA levels in the nucleus accumbens decreased significantly, reaching the maximum of 26.6 +/- 9.6% below baseline levels 120 min after mCPP (1 mg/kg i.p.) administration, and of 25.2 +/- 5.5% 140 min after MK 212 (1 mg/kg i. p.) injection. DA outflow in the striatum was unaffected by both drugs. The inhibitory effect of both mCPP and MK 212 on VTA DA cell activity was blocked completely by pretreatment with the selective 5-HT(2C) antagonist SB 242084 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline (200 microg/kg), given intravenously 10 min before the first injection of the 5-HT(2C/2B) agonists. SB 242084 (2.5 mg/kg i.p.) antagonized also the decrease in DA release induced by mCPP and MK 212 in the nucleus accumbens. Taken together, these data indicate that mCPP and MK 212 selectively inhibit mesolimbic dopaminergic function by acting on 5-HT(2C) receptors. Therefore, selective 5-HT(2C) receptor agonists might be useful in clinical conditions where it is necessary to reduce the mesolimbic dopaminergic activity without affecting the nigrostriatal function. Copyright 2000 Wiley-Liss, Inc.

PMID: 10579808, UI: 20047130

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>>> "The present data suggest that mCPP elicits a compound stimulus which is mediated by agonist interactions at the 5-HT2C receptor and possibly additional interactions with 5-HT2A, 5-HT3, and/or 5-HT1B receptors."

Psychopharmacology (Berl) 1995 Dec;122(3):237-43

5-HT2C receptor-mediated phosphoinositide turnover and the stimulus effects of m-chlorophenylpiperazine.

Fiorella D, Helsley S, Rabin RA, Winter JC

Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, USA.

The present study was designed to investigate the hypothesis that agonist interactions at 5-HT2C receptors mediate the discriminative stimulus properties of m-chlorophenylpiperazine (mCPP). Three structural classes of compounds have been described to stimulate increases in phosphoinositide (PI) hydrolysis at the 5-HT2C receptor site: phenylpiperazines, phenylalkylamines, and indolamines. Four representative phenylpiperazines, mCPP, TFMPP, MK-212 and quipazine, one phenylalkylamine, (-)DOM, and one indolamine, LSD, were employed in the present study. The efficacies of these compounds were defined (1) in vitro, with respect to their abilities to stimulate increases in PI hydrolysis in the choroid plexus, and (2) in vivo with respect to their abilities to substitute for the mCPP discriminative stimulus. In vitro intrinsic activity at the 5-HT2C site was expressed as a fraction of the maximal PI hydrolysis response elicited by serotonin (5-HT). MK-212 (fractional efficacy = 1.1) and (-)DOM (0.77) were full agonists, while mCPP (0.72), LSD (0.27), quipazine (0.24), and TFMPP (0.22) were partial agonists with respect to the stimulation of PI hydrolysis at the 5-HT2C receptor. In vivo, each of the phenylpiperazines fully substituted for the mCPP stimulus, while (-)DOM (75%), and LSD (67%) elicited only partial substitution. While compounds with agonist activity at the 5-HT2C receptor in vitro substitute for the mCPP stimulus in vivo, no clear

relationship exists between in vitro intrinsic activity at the 5-HT<sub>2C</sub> receptor with respect to the stimulation of PI turnover and maximal substitution for the mCPP stimulus in vivo. The present data suggest that mCPP elicits a compound stimulus which is mediated by agonist interactions at the 5-HT<sub>2C</sub> receptor and possibly additional interactions with 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, and/or 5-HT<sub>1B</sub> receptors.

PMID: 8748393, UI: 96353327

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>>> "DOI and mCPP, but not 6-chloro-2-[1-piperazinyl]-pyrazine, elicited a dose-dependent head-twitch response (HTR)."

J Pharmacol Exp Ther 1997 Aug;282(2):699-706

Direct injection of 5-HT<sub>2A</sub> receptor agonists into the medial prefrontal cortex produces a head-twitch response in rats.

Willins DL, Meltzer HY

Department of Psychiatry, Case Western Reserve University, School of Medicine, Cleveland, Ohio, USA.

The serotonin (5-HT)<sub>(2A/2c)</sub> agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), the 5-HT<sub>2C</sub> agonist 6-chloro-2-[1-piperazinyl]-pyrazine and the 5-HT<sub>2A</sub> partial agonist m-chloro-phenylpiperazine (mCPP) were injected bilaterally into the medial prefrontal cortex of male rats. DOI and mCPP, but not 6-chloro-2-[1-piperazinyl]-pyrazine, elicited a dose-dependent head-twitch response (HTR). DOI-induced HTR had an ED<sub>50</sub> of 12.8 nmoles/0.5 microl/side and was inhibited by the 5-HT<sub>2A</sub> antagonists ketanserin and MDL 100,907 but was not blocked by pretreatment with the selective 5-HT<sub>(2C/2B)</sub> antagonist SDZ SER 082. The HTR to mCPP demonstrated a bell-shaped dose-response curve with an ED<sub>50</sub> of 1.5 nmoles/0.5 microl/side and a peak effect after 3 nmoles/side. The response to mCPP was greatly diminished by both ketanserin and MDL 100,907 and was partially reversed by SDZ SER 082. These findings suggest that the HTR produced by the direct injection of serotonergic agonists into the medial prefrontal cortex is, in part, mediated by the activation of 5-HT<sub>2A</sub> receptors. Pretreatment of rats with the 5-HT<sub>1A</sub> agonist (+/-)-8-hydroxy-dipropylaminotetralin hydrobromide inhibited the HTR to DOI. This is consistent with other evidence that suggests a functional antagonism between 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptor activation. The HTR to DOI was potentiated by the novel 5-HT<sub>1A</sub> selective antagonist WAY 100,635, which suggests that 5-HT<sub>1A</sub> receptors tonically regulate this behavioral response to stimulation of cortical 5-HT<sub>2A</sub> receptors.

PMID: 9262333, UI: 97404247

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>>> "992 and trazodone attenuated 5-HT<sub>2A/2C</sub> receptor agonist-induced head-twitches in mice, indicating that these drugs had 5-HT<sub>2A</sub> receptor antagonistic activity."

Eur J Pharmacol 1997 Jun 18;329(1):27-35

Pharmacological studies on YM992, a novel antidepressant with selective serotonin re-uptake inhibitory and 5-HT<sub>2A</sub> receptor antagonistic activity.

Takeuchi H, Yatsugi S, Hatanaka K, Nakato K, Hattori H, Sonoda R, Koshiya K, Fujii M, Yamaguchi T

Neuroscience Research, Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., Tsukuba, Ibaraki, Japan.

YM992 ((S)-2-[[7-fluoro-4-indanyl]oxy]methyl]morpholine monohydrochloride) is a novel compound that has selective serotonin (5-hydroxytryptamine, 5-HT) re-uptake inhibition and 5-HT<sub>2A</sub> receptor antagonistic activity in vivo. YM992, fluoxetine and citalopram showed 5-HT uptake inhibition activity in 1-5-hydroxy-tryptophan (1-5-HTP)-treated mice. YM992 and trazodone attenuated 5-HT<sub>2A/2C</sub> receptor agonist-induced head-twitches in mice, indicating that these drugs had 5-HT<sub>2A</sub> receptor antagonistic activity. YM992 and amitriptyline were highly active in the mouse tail suspension test. In contrast,

fluoxetine and citalopram showed only a tendency to reduce the immobility time. Single treatment with YM992 as well as trazodone and fluoxetine ameliorated the learning deficit of olfactory-bulbectomized rats, whereas citalopram and amitriptyline showed an ameliorative effect only after chronic treatment. Although YM992 has moderate affinity for alpha1-adrenoceptors, alpha1-adrenoceptor antagonism of YM992 in vivo was 10 times weaker than that of trazodone. These results demonstrate that YM992 has 5-HT uptake inhibition and 5-HT2A receptor antagonistic activity in vivo, and suggest that YM992 may be a novel antidepressant with high efficacy in clinical use.

PMID: 9218680, UI: 97361719

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>>> "The present results suggest that the discriminative stimulus effects of mCPP in rats are mediated primarily by postsynaptic 5-HT2C receptors."

Eur J Pharmacol 1994 May 12;257(1-2):27-38

Involvement of 5-HT2C receptors in mediating the discriminative stimulus properties of m-chlorophenylpiperazine (mCPP).

Callahan PM, Cunningham KA

University of Texas Medical Branch, Department of Pharmacology and Toxicology, Galveston 77555-1031.

Rats were trained to discriminate the 5-HT receptor agonist m-chlorophenylpiperazine (mCPP; 1 mg/kg) from saline using a two-lever, water-reinforced drug discrimination task. The antidepressant trazodone (1-8 mg/kg), the 5-HT1B/2C receptor agonists 1-(m-trifluoromethylphenyl)piperazine (TFMPP; 0.25-1 mg/kg) and MK 212 (0.125-1 mg/kg), and the mixed 5-HT1A/B receptor agonist RU 24969 (0.25-2 mg/kg) substituted fully for mCPP. The 5-HT2A/2C receptor agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; 0.25-1 mg/kg) and d-lysergic acid diethylamide (LSD; 0.02-0.08 mg/kg) and the 5-HT releaser fenfluramine (0.5-2 mg/kg) also mimicked mCPP. Agonists selective for the 5-HT1A or 5-HT3 receptor or the 5-HT reuptake site produced saline-lever responding. The ergoline derivative mesulergine (0.5-4 mg/kg) produced a partial agonist/antagonist profile. The 5-HT1/2 receptor antagonist metergoline (0.125-1 mg/kg) completely blocked the mCPP cue whereas the 5-HT2A/2C receptor antagonists ketanserin and LY 53857 as well as all other 5-HT receptor antagonists failed to block the mCPP cue. The dopamine receptor antagonists SCH 23390 and haloperidol were also ineffective mCPP antagonists. Following pretreatment with the 5-HT synthesis inhibitor p-chlorophenylalanine (pCPA; 100 mg/kg/day) for 3 consecutive days, the discriminability of low doses of mCPP increased, whereas the effects of fenfluramine decreased. The present results suggest that the discriminative stimulus effects of mCPP in rats are mediated primarily by postsynaptic 5-HT2C receptors.

PMID: 8082704, UI: 94364394

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>>> "DOI is an hallucinogen having high affinity and selectivity as an agonist at 5-HT2A/2C receptors [like mCPP]... [fluoxetine was among compounds which] had either inconsistent or no effect on the DOI-induced behaviors... . . . The data show that antipsychotic agents, as a drug class, effectively block the effects of DOI. "

Prog Neuropsychopharmacol Biol Psychiatry 1999 Apr;23(3):533-44

Selectivity of action of typical and atypical anti-psychotic drugs as antagonists of the behavioral effects of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI).

Wettstein JG, Host M, Hitchcock JM

CNS Research, Hoechst Marion Roussel, Bridgewater, New Jersey, USA.  
joseph.wettstein@hmrag.com

1. There has been considerable research in the field of schizophrenia over the past few years with emphasis on the discovery of better drugs, particularly those with 5-HT2 antagonist activity. 2. In an effort to enhance identification of such compounds



and to further understand the contribution of 5-HT<sub>2</sub> activity to the effects of antipsychotic drugs, a series of conventional, atypical and purported antipsychotic compounds were assessed as antagonists of DOI-induced behaviors in rats. 3. DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) is an hallucinogen having high affinity and selectivity as an agonist at 5-HT<sub>2A/2C</sub> receptors. Over a 30-min period after injection, DOI (0.3-10.0 mg/kg; i.p.) produced dose-related behavioral effects including head-and-body shakes, forepaw tapping and skin-jerks. Effects of the antipsychotic drugs and other compounds (30 min pretreatment; i.p.) were examined against a fixed dose of DOI (3.0 mg/kg). 4. In a dose-dependent manner, M100907 (MDL 100,907), risperidone, haloperidol, clozapine, iloperidone, olanzapine, amperozide, remoxipride, ritanserin and the neurotensin agonist NTL (N alpha MeArg-Lys-Pro-Trp-Tle-Leu) antagonized each of the three behavioral effects of DOI. Drugs attenuating the head-and-body shakes were equally effective in blocking both forepaw tapping and skin-jerks indicating that these behaviors are mediated by similar mechanisms. The following compounds had either inconsistent or no effect on the DOI-induced behaviors: SB 200646A, citalopram, imipramine, fluoxetine, morphine, CP 99994, diazepam, ondansetron and SKF 97541. 5. The data show that antipsychotic agents, as a drug class, effectively block the effects of DOI. These actions are selective, as a series of nine non-antipsychotic and centrally-acting drugs were generally inactive in the procedure.

PMID: 10378235, UI: 99305998

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>>> "Although it has not yet been demonstrated that mCPP and TFMPP are agonists at central 5-HT<sub>2A</sub> receptors, this possibility should be considered when evaluating in vivo effects of these drugs."

J Pharmacol Exp Ther 1994 Nov;271(2):1122-6

m-chlorophenylpiperazine and m-trifluoromethylphenylpiperazine are partial agonists at cloned 5-HT<sub>2A</sub> receptors expressed in fibroblasts.

Grotewiel MS, Chu H, Sanders-Bush E

Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee.

Serotonin<sub>2A</sub> (5-HT<sub>2A</sub>) and 5-HT<sub>2C</sub> receptors share numerous pharmacological properties. Two compounds thought to discriminate between these two receptor subtypes are m-chlorophenylpiperazine (mCPP) and m-trifluoromethylphenylpiperazine (TFMPP). These two drugs have been classified as antagonists at 5-HT<sub>2A</sub> receptors but as agonists at 5-HT<sub>2C</sub> receptors on the basis of phosphoinositide hydrolysis studies in cerebral cortex and choroid plexus, respectively. To determine more fully the properties of mCPP and TFMPP at 5-HT<sub>2A</sub> receptors, NIH 3T3 fibroblasts transfected with the 5-HT<sub>2A</sub> receptor complementary DNA (GF6 cells) were used as a model system of receptor function. These cells express approximately 15-fold higher 5-HT<sub>2A</sub> receptor density than is found in cerebral cortex. In GF6 cells, mCPP and TFMPP dose-dependently stimulated phosphoinositide hydrolysis with maximal effects less than that of 5-HT. This agonist activity was blocked by 5-HT<sub>2A</sub> receptor antagonists but not by prior treatment with pertussis toxin. Partial inactivation of 5-HT<sub>2A</sub> receptors with phenoxybenzamine decreased the maximal effects of mCPP and TFMPP but did not eliminate agonist activity. Thus mCPP and TFMPP are partial agonists at 5-HT<sub>2A</sub> receptors in GF6 cells, and these agonist properties are retained even under conditions where receptor density is comparable to that of cerebral cortex. Although it has not yet been demonstrated that mCPP and TFMPP are agonists at central 5-HT<sub>2A</sub> receptors, this possibility should be considered when evaluating in vivo effects of these drugs.

PMID: 7965773, UI: 95055150

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>>> "The principle of the SDAs [antipsychotics] is that the drug should be a potent serotonin 5-HT<sub>2A</sub> antagonist, with slightly less potent dopamine D<sub>2</sub> receptor-blocking properties."

J Clin Psychopharmacol 1995 Feb;15(1 Suppl 1):4S-10S

The evolution of the serotonin-dopamine antagonist concept.

Huttunen M

Department of Psychiatry, Helsinki University, Finland.

Before the dopamine hypothesis of schizophrenia became established, a serotonin (5-hydroxy-tryptamine) 5-HT hypothesis was popular. This was based on the hallucinogenic properties of lysergic acid diethylamide and abnormal serotonin levels in schizophrenics. Suggestions that serotonin might be involved in the cause of schizophrenia or could be a target for antipsychotic drug action began with the discovery that the antipsychotic agent clozapine is a potent serotonin 5-HT<sub>2A</sub> antagonist, as well as being a dopamine D<sub>2</sub> antagonist. This led to the formulation of the serotonin-dopamine antagonist (SDA) concept for antipsychotics, with wider spectrums of activity and lower extrapyramidal side effects (EPS) liability. The principle of the SDAs is that the drug should be a potent serotonin 5-HT<sub>2A</sub> antagonist, with slightly less potent dopamine D<sub>2</sub> receptor-blocking properties. The clinical experience with risperidone, the first member of the new class of antipsychotics, seems to offer the promise that the SDAs have significant advantages over both the conventional dopamine-blocking neuroleptics and the atypical antipsychotic clozapine. Risperidone has efficacy against both the positive and negative symptoms of schizophrenia and has a low tendency to produce EPS. Only time will tell whether other SDAs will have the same advantages.

Publication Types: Review Review, tutorial

PMID: 7730499, UI: 95247942

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>>> "mCPP had a relative efficacy of 65% at 5-HT<sub>2C</sub> receptors but <25% at either 5-HT<sub>2A</sub> or 5-HT<sub>2B</sub> receptors."

Br J Pharmacol 1999 Sep;128(1):13-20

Functional characterization of agonists at recombinant human 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors in CHO-K1 cells.

Porter RH, Benwell KR, Lamb H, Malcolm CS, Allen NH, Revell DF, Adams DR, Sheardown MJ

Cerebrus Ltd, Oakdene Court, 613 Reading Road, Winnersh, Wokingham, RG41 5UA.  
r.porter@cerebrus.ltd.uk

1. The goal of this study was to characterize the agonist pharmacology of human 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> (VSV) receptors expressed in CHO-K1 (Chinese hamster ovary) cells. 2. We used a fluorometric imaging plate reader (FLIPR) which allows rapid detection of rises in intracellular calcium levels upon the addition of agonists. 3. Stimulation of all three receptors by 5-HT caused a robust concentration dependent increase in intracellular calcium levels. No such effect was observed from non-transfected control CHO-K1 cells. 4. The rank order of potency of agonists at the different receptor subtypes varied. Tryptamines, BW-723C86, d-norfenfluramine, Ro 60-0175 and LSD exhibited the following rank order of potency; 5-HT<sub>2B</sub>>5-HT<sub>2C</sub>>5-HT<sub>2A</sub>. Piperazines such as m-Chlorophenylpiperazine (mCPP), ORG-12962, MK-212 and also ORG-37684 exhibited a rank order of potency of 5-HT<sub>2C</sub>>5-HT<sub>2B</sub>>5-HT<sub>2A</sub>. The phenylisopropylamines DOI and DOB had a rank order of 5-HT<sub>2A</sub>>5-HT<sub>2B</sub>>5-HT<sub>2C</sub>. 5. Many agonists tested had partial agonist actions when compared to 5-HT, and a wide range of relative efficacies were exhibited, which was cell line dependent. For example, mCPP had a relative efficacy of 65% at 5-HT<sub>2C</sub> receptors but <25% at either 5-HT<sub>2A</sub> or 5-HT<sub>2B</sub> receptors. 6. Interpretation of literature values of functional assays using different cell lines, different receptor expression levels and different receptor isoforms, is complex. Species differences and the previous use of antagonist radioligands to characterize agonist potency in binding assays emphasizes the importance of studying agonists in the same experiment using the same assay conditions and parental cell lines.

PMID: 10498829, UI: 99430059

>>> "Trazodone is a potent agonist at 5-HT2C receptors"

J Pharmacol Exp Ther 1998 Jun;285(3):983-6 Related Articles, Books, LinkOut

Trazodone is a potent agonist at 5-HT2C receptors mediating inhibition of the N-methyl-D-aspartate/nitric oxide/cyclic GMP pathway in rat cerebellum.

Marcoli M, Maura G, Tortarolo M, Raiteri M

Dipartimento di Medicina Sperimentale, Sezione di Farmacologia e Tossicologia, Università di Genova, Viale Cembrano 4, 16148 Genova, Italy.

The effects of trazodone on the cyclic GMP elevation elicited by N-methyl-D-aspartate in rat cerebellar slices were analyzed. Trazodone inhibited in a concentration-dependent manner ( $EC_{50} = 0.82$  nM) the cyclic GMP response evoked by 0.1  $\mu$ M N-methyl-D-aspartate. The inhibition was near complete at 10 nM trazodone. The effect of 10 nM trazodone was unaffected by 0.3  $\mu$ M spiperone or rauwolscine, antagonists with selectivity for the 5-HT(serotonin) $2A$  or the 5-HT $2B$  subtype, respectively, but it was totally prevented by 0.01  $\mu$ M mesulergine, a 5-HT $2A$ /5-HT $2B$ /5-HT $2C$  receptor antagonist. Trazodone was potently counteracted ( $IC_{50} = 2.7$  nM) by the selective 5-HT $2B$ /5-HT $2C$  receptor antagonist N-(1-methyl-5-indolyl)-N-(3-pyridil) urea HCl and, less potently ( $IC_{50} = 95$  nM), by ketanserin, a 5-HT $2A$ /5-HT $2C$  receptor blocker. It is concluded that trazodone behaves as a potent full agonist at the 5-HT $2C$  receptor mediating inhibition of the cerebellar N-methyl-D-aspartate/nitric oxide/cyclic GMP system.

PMID: 9618398, UI: 98283927

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## Metabolism of mCPP

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>>> "These results confirm that CYP2D6 is the isoform responsible for the p-hydroxylation of mCPP, and indicate that caution should be exercised in coprescribing inhibitors or substrates of CYP2D6 with drugs that have mCPP as a metabolite."

Biol Psychiatry 1998 Dec 1;44(11):1185-91

Human CYP2D6 and metabolism of m-chlorophenylpiperazine.

Rotzinger S, Fang J, Coutts RT, Baker GB

Department of Psychiatry, University of Alberta, Edmonton, Canada.

BACKGROUND: Metabolic drug-drug interactions can occur between drugs that are substrates or inhibitors of the same cytochrome P450 (CYP) isoenzymes, but can be prevented by knowing which isoenzymes are primarily responsible for a drug's metabolism. m-Chlorophenylpiperazine (mCPP) is a psychopharmacologically active metabolite of four different psychiatric drugs. The present experiments were designed to identify the CYP isoenzymes involved in the metabolism of mCPP to its main metabolite p-hydroxy-mCPP (OH-mCPP). METHODS: The rate of production of OH-mCPP from mCPP was correlated with isoform activities in a panel of human liver microsomes, was assessed using a panel of individual complementary DNA-expressed human CYP isoenzymes, and was investigated in the presence of a specific inhibitor of CYP2D6. RESULTS: OH-mCPP production correlated significantly with CYP2D6 activity in human liver microsomes. Furthermore, incubations with microsomes from cells expressing CYP2D6 resulted in OH-mCPP formation, whereas no mCPP was formed from incubations with microsomes from cells expressing other individual isoforms. Finally, when the specific CYP2D6 inhibitor quinidine was preincubated with either human liver microsomes or cells expressing human CYP2D6, there was a concentration-dependent decrease in the production of OH-mCPP. CONCLUSIONS: These results confirm that CYP2D6 is the isoform responsible for the p-hydroxylation of mCPP, and indicate that caution should be exercised in coprescribing inhibitors or substrates of CYP2D6 with drugs that have mCPP as a metabolite.

PMID: 9836023, UI: 99052743

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>>> "The present results indicate 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."

Drug Metab Dispos 1998 Jun;26(6):572-5

Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources.

Rotzinger S, Fang J, Baker GB

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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 microM) 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 microM) 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.

PMID: 9616194, UI: 98282258

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J Clin Pharmacol 2000 Feb;40(2):200-4

Unusually low clearance of two CYP3A substrates, alprazolam and trazodone, in a volunteer subject with wild-type CYP3A4 promoter region.

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A healthy 40-year-old Caucasian male volunteer displayed unusually low clearance and long elimination half-life of alprazolam and trazodone, two CYP3A substrate drugs, following single-dose oral administration in clinical pharmacokinetic studies. Genomic DNA isolated from the individual's peripheral blood was subjected to polymerase chain reaction amplification and subsequent sequence analysis of a 592 base-pair segment upstream from the CYP3A coding region. The analysis revealed no variation from wild-type in the nucleotide present at position -290, previously suggested to influence expression and/or activity of CYP3A. The functional significance of this promoter region mutation is unclear and requires further evaluation.

PMID: 10664927, UI: 20128312

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>>> "clearance of mCPP is mediated by P450-2D6"

Psychopharmacology (Berl) 1999 Jul;145(1):113-22

Nefazodone, meta-chlorophenylpiperazine, and their metabolites in vitro: cytochromes mediating transformation, and P450-3A4 inhibitory actions.

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**RATIONALE:** Understanding of the mechanisms of biotransformation of antidepressant drugs, and of their capacity to interact with other medications, is of direct relevance to rational clinical psychopharmacology. **OBJECTIVES:** To determine the human cytochromes P450 mediating the metabolism of nefazodone, and the inhibitory activity of nefazodone and metabolites versus human P450-3A. **METHODS:** Biotransformation of nefazodone to its metabolic products, and of meta-chlorophenylpiperazine (mCPP) to para-hydroxy-mCPP, was studied in vitro using human liver microsomes and heterologously expressed human cytochromes. Nefazodone and metabolites were also tested as inhibitors of alprazolam hydroxylation, reflecting activity of cytochrome P450-3A isoforms. **RESULTS:** mCPP and two hydroxylated derivatives were the principal metabolites formed from nefazodone by liver microsomes. Metabolite production was strongly inhibited by ketoconazole or troleandomycin (relatively specific P450-3A inhibitors), and by an anti-P450-3A antibody. Only heterologously expressed human P450-3A4 mediated formation of nefazodone metabolites from the parent compound. Nefazodone, hydroxy-nefazodone, and para-hydroxy-nefazodone were strong 3A inhibitors, being more potent than norfluoxetine and fluvoxamine, but less potent than ketoconazole. The triazolodione metabolite and mCPP had weak or negligible 3A-inhibiting activity. Formation of parahydroxy-mCPP from mCPP was mediated by heterologously expressed P450-2D6; in liver microsomes, the reaction was strongly inhibitable by quinidine, a relatively specific 2D6 inhibitor. **CONCLUSION:** The complex parallel biotransformation pathways of nefazodone are mediated mainly by human cytochrome P450-3A, whereas clearance of mCPP is mediated by P450-2D6. Nefazodone and two of its hydroxylated metabolites are potent 3A inhibitors, accounting for

pharmacokinetic drug interactions of nefazodone with 3A substrate drugs such as triazolam and alprazolam.

PMID: 10445380, UI: 99372552

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J Psychopharmacol (Oxf) 1998;12(3 Suppl B):S89-97

Debate resolved: there are differential effects of serotonin selective reuptake inhibitors on cytochrome P450 enzymes.

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In 1993, it was first proposed that an important difference between selective serotonin reuptake inhibitors (SSRIs) was the degree of inhibition of the cytochrome P450 (CYP) enzyme 2D6 that they produced under usually dosing conditions (Preskorn, 1993). Specifically, fluoxetine and paroxetine, in contrast to sertraline, were identified as causing substantial increases in the plasma levels of coadministered drugs, which were principally dependent on CYP 2D6 for their metabolism. Over the next 5 years, this position was hotly contested (Preskorn and Nemeroff, 1997). However, an extensive body of research has now accumulated, which incontrovertibly supports the original position. This paper will review this research and extend the discussion to all five SSRIs and four other important CYP enzymes: 1A2, 2C9/10, 2C19, and 3A3/4.

Publication Types: Review Review, tutorial

PMID: 9808080, UI: 99023266

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>>> "A large number of drugs (including beta blockers, antiarrhythmics, tricyclic antidepressants, and neuroleptics) are substrates for CYP2D6, and a 10- to 20-fold difference in metabolism of some of these drugs accounts for the interest in this polymorphism"

Medscape Practical Pharmacology

<http://primarycare.medscape.com/SCP/IIM/1996/v13.n06/m1739.rodvold/m1739.rodvold.html>

The biotransformations of debrisoquine and mephenytoin, on the other hand, exhibit polymorphisms of the cytochrome P-450 system. A deficiency in debrisoquine hydroxylase activity in a subset of the population is accounted for by altered CYP2D6 enzyme activity. In the Caucasian population, about 7% to 10% of individuals are deficient in this enzyme and therefore are poor metabolizers.[7] A large number of drugs (including beta blockers, antiarrhythmics, tricyclic antidepressants, and neuroleptics) are substrates for CYP2D6, and a 10- to 20-fold difference in metabolism of some of these drugs accounts for the interest in this polymorphism.[6]

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>>> "The present study thus suggests that the CYP2D6 genotype cannot predict the C<sub>ss</sub> of these compounds [trazodone and mCPP]."

Psychopharmacology (Berl) 1997 Sep;133(1):95-8

Relationship between the CYP2D6 genotype and the steady-state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine.

Mihara K, Otani K, Suzuki A, Yasui N, Nakano H, Meng X, Ohkubo T, Nagasaki T, Kaneko S, Tsuchida S, Sugawara K, Gonzalez FJ

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The relationship between the cytochrome P450 (CYP) 2D6 genotype and the steady-state plasma concentrations (Css) of trazodone and its active metabolite m-chlorophenylpiperazine (mCPP) was studied in 54 depressed Japanese patients receiving trazodone 150 mg at bedtime. By use of allele-specific PCR analysis, the wild type allele, three mutated alleles causing absent enzyme activity (CYP2D6A, CYP2D6B and CYP2D6D) and one mutated allele causing decreased enzyme activity (CYP2D6 Ch) were identified. The means (ranges) of the Css of trazodone, corrected to the median body weight in 17 cases with no mutated allele, 27 cases with one mutated allele and 10 cases with two mutated alleles, were 556 (281-1115), 643 (302-1362) and 671 (234-1418) ng/ml, respectively, while the values of mCPP were 60 (35-121), 65 (33-99) and 58 (38-112) ng/ml, respectively. Neither the Css of trazodone (F = 0.80, P = 0.45) nor that of mCPP (F = 0.49, P = 0.61) significantly differed among the three groups. The present study thus suggests that the CYP2D6 genotype cannot predict the Css of these compounds.

PMID: 9335086, UI: 97475574

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>>> "Smokers had significantly (p < 0.05) lower plasma concentrations of trazodone and higher mCPP/trazodone ratios than non-smokers."

Int Clin Psychopharmacol 1995 Sep;10(3):143-6

Effects of various factors on steady state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine.

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Effects of various factors on steady state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine (mCPP) were studied in 43 depressed patients (19 males, 24 females) receiving trazodone 150 mg at bedtime for 1-3 weeks. Sixteen cases were smokers, and 19 cases were also receiving various benzodiazepines. The means (and ranges) of plasma concentrations of trazodone and mCPP, and the mCPP/trazodone ratio were 619 (251-1059) ng/ml, 59 (32-139) ng/ml and 0.100 (0.044-0.219), respectively. Smokers had significantly (p < 0.05) lower plasma concentrations of trazodone and higher mCPP/trazodone ratios than non-smokers. Age, sex and co-administration of benzodiazepines did not affect any plasma concentrations or the mCPP/trazodone ratio. In 11 cases where the dose was increased to 300 mg, neither plasma concentration/dose ratios nor the mCPP/trazodone ratio changed significantly. The present study thus suggests that: (1) there is a large Interindividual variation in the metabolism of trazodone; (2) smoking enhances the metabolism, but age, sex and co-administration of benzodiazepines do not affect it; (3) trazodone and mCPP have linear kinetics.

PMID: 8675966, UI: 96115705