

Selections from a literature search on side effects, drug-drug interaction, and metabolic deficiencies in CYP2D6 activity relating to Fluoxetine, Norfluoxetine, Trazodone, and mCPP, with references.

Kevin Eric Saunders a/k/a bonze blayk(5/24/00)

- >>> "The effects of the TCAs on INa are similar to local anesthetic behavior"
- >>> "Trazodone ... [has] ... an antinociceptive activity. It is stressed that this activity has been of critical importance in the discovery of trazodone. In fact, the development of this drug was based on the working hypothesis that a disturbance in the perception of unpleasant experience has a role in the pathogenesis of depression."
- >>> "Caution in prescribing trazodone and in the cardiac monitoring of patients receiving trazodone is recommended."
- >>> "Patients receiving a tricyclic antidepressant should be monitored closely for toxicity if a SSRI-type drug is added. Clinicians should be particularly cautious in patients with fluoxetine due to the extremely long elimination half-life of its metabolite, norfluoxetine (7-9 days)."
- >>> "Data from studies on trazodone and fluoxetine suggest that lower dosages may prove as effective (if not more effective) than very high dosages.... Side effects of fluoxetine and fluvoxamine include primarily nausea, weight loss, insomnia, and anxiety."
- >>> "poor metabolizers accumulate fluoxetine but not sertraline and that CYP2D6 plays an important role in the demethylation of fluoxetine but not of sertraline"
- >>> "Potent inhibition of cytochrome P450 2D6(CYP2D6) in human liver microsomes by fluoxetine and its major metabolite norfluoxetine was confirmed.... Inhibition of CYP2D6 activity in patients undergoing treatment with fluoxetine or other serotonin uptake inhibitors could contribute to toxicity or attenuated response from concurrent medications that are substrates of this enzyme."
- >>> **"The rate of deficiency in CYP2D6 expression in these Caucasian state psychiatric hospital patients (14%) was twice that of the U.S. population (7%)."**
- >>> "fluoxetine and norfluoxetine are potent inhibitors of CYP2D6... This can give rise to drug-drug interactions that may have no effect, lead to intoxication, or improve the therapeutic response"
- >>> "SSRIs are potent inhibitors of the hepatic isoenzyme P450-2D6 and would be expected to have effects on the clearance of drugs metabolized by this enzyme."
- >>> "CYP2D6 is inhibited by SSRIs, in order of decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram and fluvoxamine. This may have clinical consequences with some but not all SSRIs, when they are taken with tricyclic antidepressants.... There have been many reports on marked pharmacokinetic interactions between fluoxetine and tricyclic antidepressants."
- >>> "norfluoxetine is more potent than fluoxetine as an inhibitor of CYP3A3/4, and in view of the longer half-life (t1/2) of the metabolite the potential for interactions may persist for weeks after discontinuation of the parent drug"
- >>> "fluoxetine, largely via its metabolite norfluoxetine, may impair clearance of P450-3A substrates"
- >>> "norfluoxetine was the only potent inhibitor of CYP3A"
- >>> Lilly reports "fluoxetine and norfluoxetine together would inhibit CYP3A catalytic activity by less than 7%" -- [DISAGREES WITH OTHER RESULTS]

>> Fluoxetine -> Cytochrome P450-2C9      Norfluoxetine

## References from a literature search on side effects of Fluoxetine, and drug-drug interaction and metabolic deficiencies in CYP2D6 activity relating to Fluoxetine, Norfluoxetine, Trazodone, and mCPP.

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>>> "The effects of the TCAs on INa are similar to local anesthetic behavior"

<<http://jpet.aspetjournals.org/cgi/content/full/284/1/208>>

Inhibition of neuronal Na<sup>+</sup> channels by antidepressant drugs.

Pancrazio JJ, Kamatchi GL, Roscoe AK, Lynch C3rd

Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, USA.

Although tricyclic antidepressant (TCA) blockade of cardiac Na<sup>+</sup> channels is appreciated, actions on neuronal Na<sup>+</sup> channels are less clear. Therefore, the effects of TCAs (amitriptyline, doxepin and desipramine) as well as trazodone and fluoxetine on voltage-gated Na<sup>+</sup> current (INa) were examined in bovine adrenal chromaffin cells using the whole-cell patch-clamp method. Amitriptyline produced concentration-dependent depression of peak INa evoked from a holding potential of -80 mV with KD value of 20.2 microM and a Hill coefficient of 1.2. Although 20 microM amitriptyline induced no change in the rate or voltage dependence of INa activation, steady-state inactivation demonstrated a 15-mV hyperpolarizing shift. Similar results were observed for doxepin and desipramine. This shift in steady-state inactivation was associated with a slowed rate of recovery from the inactivated state. Contrasting results were observed with the atypical antidepressants: while 20 microM fluoxetine depressed peak INa by 61% and caused a 7-mV hyperpolarizing shift in steady-state inactivation, 100 microM trazodone decreased peak INa by only 19% and caused only a 3-mV shift. Although the magnitude of fluoxetine effects was similar to those of the TCAs, the onset of fluoxetine effects was substantially slower than for amitriptyline. In voltage-clamp and current-clamp measurements from neonatal rat dorsal root ganglion neurons, 20 microM amitriptyline decreased INa by 52% and depressed action potential dynamics consistent with enhanced Na<sup>+</sup> channel inactivation. The effects of the TCAs on INa are similar to local anesthetic behavior and could contribute to certain analgesic actions.

PMID: 9435180, UI: 98102629

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>>> "Trazodone ... [has] ... an antinociceptive activity. It is stressed that this activity has been of critical importance in the discovery of trazodone. In fact, the development of this drug was based on the working hypothesis that a disturbance in the perception of unpleasant experience has a role in the pathogenesis of depression."

Psychopathology 1984;17 Suppl 2:3-14

Trazodone, a new avenue in the treatment of depression.

Silvestrini B, Valeri P

Pharmacological and biochemical data on trazodone are reviewed in order to compare this drug to imipramine and other tricyclics both from the point of view of the mechanism of action and preferential clinical indications. Trazodone tends to inhibit biochemical and pharmacological functions depending on the catecholaminergic system, whereas imipramine has a potentiating activity. However, both these drugs decrease the density of beta-receptors following repeated administrations. Trazodone and imipramine have similar effects on the serotonergic system. The two drugs also share an antinociceptive activity. It is stressed that this activity has been of critical

importance in the discovery of trazodone. In fact, the development of this drug was based on the working hypothesis that a disturbance in the perception of unpleasant experience has a role in the pathogenesis of depression. Some medical implications of the alpha-blocking activity of trazodone are discussed. Trazodone is preferable to other antidepressant treatment when depression is associated with angle-closure glaucoma, cardiovascular disturbances depending on noradrenaline release, tremor, some psychotic conditions and alcoholism.

PMID: 6144138, UI: 84194905

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Can J Physiol Pharmacol 1997Aug;75(8):983-7

Atypical antidepressants inhibit depolarization-induced calcium uptake in rat hippocampus synaptosomes.

Lavoie PA, Beauchamp G, Elie R

Departement de pharmacologie, Universite deMontreal, QC, Canada.

The effect of the atypical antidepressants mianserin, iprindole, and fluoxetine on synaptosomal calcium uptake was tested under conditions where a selective action on voltage-dependent calcium channels can be documented. Synaptosomes from rat hippocampus were incubated with 45calcium either in choline-rich medium or in depolarizing (60 mM K+) choline-rich medium, and drug effects on calcium uptake in these two conditions, as well as on the net depolarization-induced calcium uptake, were studied in the range of concentrations 0.6-200 microM. A concentration-dependent marked inhibition of uptake in depolarizing choline medium was observed for the three antidepressants, whereas only a minor degree of inhibition of uptake in resting choline medium was present at the highest drug concentration; as a result, the concentration-effect relationships exhibited a strong concentration-dependent inhibition of net depolarization-induced calcium uptake. The IC50 values, calculated by interpolation of the last three or four points of the concentration-effect relationships, were 27, 39, and 68 microM for fluoxetine, iprindole, and mianserin, respectively. Significant degrees of calcium channel inhibition are not expected at brain concentrations of mianserin and iprindole that are likely to be encountered during clinical use; however, the fluoxetine concentration-effect relationship established in the present study, coupled with the published ratio of 20:1 for brain:plasma concentrations of fluoxetine-norfluoxetine in humans, suggests that brain calcium channel function could be appreciably reduced in some patients treated with this atypical antidepressant.

PMID: 9360012, UI: 98024313

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>>> "Caution in prescribing trazodone and in the cardiac monitoring of patients receiving trazodone is recommended."

J Clin Psychiatry 1986 Jul;47(7):388-9

A case of trazodone-induced ventricular tachycardia.

Aronson MD, Hafez H

Trazodone was associated with the occurrence of life-threatening premature ventricular contractions and angina in a 45-year-old white man who had no prior cardiovascular disease. Caution in prescribing trazodone and in the cardiac monitoring of patients receiving trazodone is recommended.

PMID: 2424891, UI: 86250660

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>>> "Patients receiving a tricyclic antidepressant should be monitored closely for toxicity if a SSRI-type drug is added. Clinicians should be particularly cautious in patients with fluoxetine due to the extremely long elimination half-life of its metabolite, norfluoxetine (7-9 days)."

<http://www.migraines.org/treatment/amitrip.htm>

Clinicians should be alert for pharmacokinetic interactions between tricyclic antidepressants and the selective serotonin reuptake inhibitors (SSRIs) class of antidepressants. The SSRIs are known to inhibit isozymes of the cytochrome P-450 mixed-function oxidase system including CYP2D6 and/or CYP3A4, the isozymes responsible for metabolism of many of the tricyclic antidepressants. Cytochrome CYP2D6 is impaired most by fluoxetine and least by sertraline and is the isozyme most responsible for metabolism of tricyclic antidepressants. In several cases, symptoms of toxicity, including seizures, were reported when drugs from these 2 categories were used together. At least one case report exists of a death thought to be due to impaired clearance of amitriptyline by fluoxetine. The CYP2D6 isozyme is a common pathway for both of these drugs and norfluoxetine also inhibits this enzyme. Patients receiving a tricyclic antidepressant should be monitored closely for toxicity if a SSRI-type drug is added. Clinicians should be particularly cautious in patients with fluoxetine due to the extremely long elimination half-life of its metabolite, norfluoxetine (7-9 days).

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>>> "Data from studies on trazodone and fluoxetine suggest that lower dosages may prove as effective (if not more effective) than very high dosages.... Side effects of fluoxetine and fluvoxamine include primarily nausea, weight loss, insomnia, and anxiety."

J Clin Psychopharmacol 1987 Dec;7(6Suppl):44S-49S

Recent studies on selective serotonergic antidepressants: trazodone, fluoxetine, and fluvoxamine.

Schatzberg AF, Dessain E, O'Neil P, Katz DL, Cole JO

Affective Disease Program, McLean Hospital, Belmont, MA 02178.

In recent years, the role of serotonin in the pathophysiology of depressive disorders has been intensively studied. These studies have been complemented by the development of newer antidepressant agents that exert specific effects on serotonin systems. This paper reviews the pharmacology of these newer compounds and contrasts it with those of the standard tricyclic antidepressants. The current status of various serotonergic agents is discussed. Results are reviewed from recent double-blind studies comparing three compounds (trazodone, fluoxetine, and fluvoxamine) to a standard tricyclic antidepressant. Relative efficacy, dropout rates, optimal dosages, and side effects are emphasized. Data from studies on trazodone and fluoxetine suggest that lower dosages may prove as effective (if not more effective) than very high dosages. Implications of these data are discussed. Side effects of fluoxetine and fluvoxamine include primarily nausea, weight loss, insomnia, and anxiety. Possible application of specific serotonin reuptake blockers in the treatment of obsessive-compulsive disorder and in the reduction of alcohol consumption is also reviewed.

Publication Types: Review Review, tutorial

PMID: 3123528, UI: 88116146

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J Child Adolesc Psychopharmacol 2000Spring;10(1):27-34

Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency.

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salleefr@email.uc.edu

[Medline record in process]

The clinical course of a 9-year-old diagnosed with attention-deficit hyperactivity

disorder, obsessive-compulsive disorder, and Tourette's disorder and treated with a combination of methylphenidate, clonidine, and fluoxetine is described. The patient experienced over a 10-month period, signs and symptoms suggestive of metabolic toxicity marked by bouts of gastrointestinal distress, low-grade fever, incoordination, and disorientation. Generalized seizures were observed, and the patient lapsed into status epilepticus followed by cardiac arrest and subsequently expired. At autopsy, blood, brain, and other tissue concentrations of fluoxetine and norfluoxetine were several-fold higher than expected based on literature reports for overdose situations. The medical examiner's report indicated death caused by fluoxetine toxicity. As the child's adoptive parents controlled medication access, they were investigated by social welfare agencies. Further genetic testing of autopsy tissue revealed the presence of a gene defect at the cytochrome P450 CYP2D locus, which results in poor metabolism of fluoxetine. As a result of this and other evidence, the investigation of the adoptive parents was terminated. This is the first report of a fluoxetine-related death in a child with a confirmed genetic polymorphism of the CYP2D6 gene that results in impaired drug metabolism. Issues relevant to child and adolescent psychopharmacology arising from this case are discussed.

PMID: 10755579, UI: 20216355

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Pharmacogenetics 1999 Feb;9(1):55-60

The stereoselective metabolism of fluoxetine in poor and extensive metabolizers of sparteine.

Fjordside L, Jeppesen U, Eap CB, Powell K, Baumann P, Brosen K

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The selective serotonin reuptake inhibitor fluoxetine is administered as a racemic mixture, and R- and S-fluoxetine are metabolized in the liver by N-demethylation to R- and S-norfluoxetine, respectively. R- and S-fluoxetine and S-norfluoxetine are equally potent selective serotonin reuptake inhibitors, but R-norfluoxetine is 20-fold less potent in this regard. Racemic fluoxetine and norfluoxetine are potent inhibitors of cytochrome P450 (CYP) 2D6 in vivo and in vitro and recent studies in vivo have shown that racemic fluoxetine is metabolized by CYP2D6. The primary aim of the present study was to investigate the stereoselective metabolism of fluoxetine and norfluoxetine by CYP2D6 in vivo. A single oral dose of fluoxetine (60 mg) was administered to six poor and six extensive metabolizers of sparteine. Blood samples were collected during 6 weeks for poor metabolizers and 3 weeks for extensive metabolizers. Once a week a sparteine test was performed. The R- and S-enantiomers of fluoxetine and norfluoxetine were determined by a stereoselective gaschromatography-mass spectroscopy method. In the poor metabolizers, the oral clearance of R- and S-fluoxetine was 3.0 l/h and 17 l/h, respectively, the corresponding values in the extensive metabolizers were 36 l/h and 40 l/h, respectively. For both enantiomers, the phenotype difference was statistically significant. In poor metabolizers, the elimination half-lives were 6.9 days and 17.4 days for R- and S-norfluoxetine, respectively, and in the extensive metabolizers it was 5.5 days for both enantiomers, a significant phenotypical difference only for S-norfluoxetine. For fluoxetine the elimination half-lives were 9.5 and 6.1 days in poor metabolizers for the R- and S-enantiomer, respectively. The corresponding values in the extensive metabolizers were 2.6 and 1.1 days, respectively. Also for this parameter, the differences were statistically significant. This study shows that CYP2D6 catalyses the metabolism of R- and S-fluoxetine and most likely the further metabolism of S-norfluoxetine but not of R-norfluoxetine.

Publication Types: Clinical trial

PMID: 10208643, UI: 99223342

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Clin Pharmacol Ther 1996 Nov;60(5):522-34

The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry.

Chen S, Chou WH, Blouin RA, Mao Z, Humphries LL, Meek QC, Neill JR, Martin WL, Hays LR, Wedlund PJ

Division of Pharmacology and Experimental Therapeutics, College of Pharmacy, University of Kentucky, Lexington 40536-0082, USA.

**OBJECTIVES:** This study examined factors that affect cost, reliability, and the value of determining the cytochrome P4502D6 (CYP2D6) polymorphism in clinical practice. **STUDY DESIGN:** The method of deoxyribonucleic acid isolation, sample preparation, oligonucleotide primers, and polymerase chain reaction procedures were scrutinized for their effect on CYP2D6 genotyping efforts. The determination of the CYP2D6 A, B, D, E, and T alleles was used to identify the deficiency in CYP2D6 expression in 161 individuals phenotyped for CYP2D6 activity with dextromethorphan. The CYP2D6 genotype was assessed in 74 outpatients who had received diagnoses of depression. Eighteen of these patients were screened because of an adverse response to a tricyclic or antidepressant known or suspected to be a CYP2D6 substrate. **RESULTS:** The CYP2D6 A, B, C, D, E, and T alleles could be detected in 13 hours at a cost of \$84 per sample by judicious selection of conditions and procedures. The genotype provided an accurate predictor of CYP2D6 expression in all 134 subjects who expressed the enzyme and in all 27 unrelated individuals phenotyped as deficient in CYP2D6 activity. In the patient group that experienced adverse effects, 44% of all CYP2D6 gene copies contained the A, B, D, E, or T allele(s) associated with inactive CYP2D6 expression. This was more than twice the rate for the occurrence of mutant alleles in the other 56 psychiatric patients (21%) and in 80 random subjects from the general population (20%;  $p < 0.05$ ). **CONCLUSIONS:** Screening psychiatric patients for CYP2D6 expression may distinguish metabolic-based therapeutic problems from drug sensitivity caused by other mechanisms.

PMID: 8941025, UI: 97096001

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>>> "poor metabolizers accumulate fluoxetine but not sertraline and that CYP2D6 plays an important role in the demethylation of fluoxetine but not of sertraline"

Clin Pharmacol Ther 1996 Nov;60(5):512-21

The disposition of fluoxetine but not sertraline is altered in poor metabolizers of desipramine.

Hamelin BA, Turgeon J, Vallee F, Belanger PM, Paquet F, LeBel M

School of Pharmacy, Universite Laval, Quebec Heart Institute, Laval Hospital, Sainte-Foy, Canada.

**BACKGROUND:** Substrates and inhibitors of the cytochrome P450 isozyme CYP2D6 have overlapping structural characteristics. Two prototype serotonin uptake inhibitors, sertraline and fluoxetine, share these structural criteria and have been identified as potent inhibitors of CYP2D6 in vitro. The current study was undertaken to investigate whether genetically determined CYP2D6 activity alters the disposition of sertraline or fluoxetine or both. **METHODS:** Single doses of sertraline (50 mg) and fluoxetine (20 mg) were administered successively to 20 young men with high (extensive metabolizers;  $n = 10$ ) and low (poor metabolizers;  $n = 10$ ) CYP2D6 activity. Blood and urine samples were collected for 5 to 7 half-lives and sertraline, desmethyl sertraline, fluoxetine, and norfluoxetine were determined by GC and HPLC techniques. **RESULTS:** Poor metabolizers had significantly greater fluoxetine peak plasma concentrations ( $C_{max}$ ; increases 57%), area under the concentration versus time curve (AUC zero-->infinity; increases 290%), and terminal elimination half-life (increases 216%) compared with extensive metabolizers. The total amount of fluoxetine excreted in the urine during 8 days was almost three times higher in poor metabolizers than in extensive metabolizers (719 versus 225 micrograms;  $p < 0.05$ ), whereas the total amount of norfluoxetine excreted in urine of poor metabolizers was about half of that of extensive metabolizers (524 versus 1047 micrograms;  $p < 0.05$ ). Norfluoxetine  $C_{max}$  and AUC zero-->t were significantly smaller in poor metabolizers (decreases 55% and decreases 53%, respectively), and the partial metabolic clearance of fluoxetine into norfluoxetine was 10 times smaller in this group ( $4.3 \pm 1.9$  versus  $0.4 \pm 0.1$  L/hr;  $p < 0.05$ ). No significant differences between group extensive and poor metabolizers were found for sertraline and desmethyl sertraline pharmacokinetics. **CONCLUSION:** These data indicate that poor metabolizers accumulate fluoxetine but not sertraline and that CYP2D6 plays an important role in the demethylation of fluoxetine but not of sertraline.

PMID: 8941024, UI: 97096000

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>>> "Potent inhibition of cytochrome P450 2D6(CYP2D6) in human liver microsomes by fluoxetine and its major metabolite norfluoxetine was confirmed.... Inhibition of CYP2D6 activity in patients undergoing treatment with fluoxetine or other serotonin uptake inhibitors could contribute to toxicity or attenuated response from concurrent medications that are substrates of this enzyme."

Clin Pharmacol Ther 1993 Apr;53(4):401-9

Inhibition by fluoxetine of cytochrome P4502D6 activity.

Otton SV, Wu D, Joffe RT, Cheung SW, SellersEM

Clinical Research and Treatment Institute,Addiction Research Foundation of Ontario, Toronto, Canada.

Potent inhibition of cytochrome P450 2D6(CYP2D6) in human liver microsomes by fluoxetine and its major metabolite norfluoxetine was confirmed (apparent inhibition constant values, 0.2µmol/L). Several other serotonergic agents were also found to be competitive inhibitors of this genetically polymorphicenzyme. The O-demethylation ratio of dextromethorphan that expressed CYP2D6activity in 19 patients receiving fluoxetine fell in the region of the antimode separating the O-demethylation ratio values observed in 208 extensive metabolizers from 15 poor metabolizers of a control group of healthy subjects. Inhibition of CYP2D6 activity in patients undergoing treatment with fluoxetine or other serotonin uptake inhibitors could contribute to toxicity or attenuated response from concurrent medications that are substrates of this enzyme. Other in vitro studies indicated that CYP2D6catalyzes the O-demethylation of oxycodone to form oxymorphone. This reaction was inhibited by fluoxetine and its normetabolite in liver microsomes from both extensive and poor metabolizer individuals, indicating that these compounds are not selective inhibitors of CYP2D6 activity.

PMID: 8477556, UI: 93238451

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Am J Hum Genet 1997 Feb;60(2):284-95

Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences.

Sachse C, Brockmoller J, Bauer S, Roots I

Institute of Clinical Pharmacology, University Clinic Charite, Humboldt University of Berlin, Germany.

Cytochrome P450 2D6 (CYP2D6) metabolizes many important drugs. CYP2D6 activity ranges from complete deficiency to ultrafast metabolism, depending on at least 16 different known alleles. Their frequencies were determined in 589 unrelated German volunteers and correlated with enzyme activity measured by phenotyping with dextromethorphan or debrisoquine. For genotyping, nested PCR-RFLP tests from a PCR amplificate of the entire CYP2D6 gene were developed. The frequency of the CYP2D6\*1 allele coding for extensive metabolizer (EM) phenotype was .364. The alleles coding for slightly (CYP2D6\*2) or moderately (\*9 and \*10) reduced activity (intermediate metabolizer phenotype [IM]) showed frequencies of .324, .018, and .015, respectively. By use of novel PCR tests for discrimination, CYP2D6 gene duplication alleles were found with frequencies of .005 (\*1x2), .013 (\*2x2), and .001 (\*4x2). Frequencies of alleles with complete deficiency (poor metabolizer phenotype[PM]) were .207 (\*4), .020 (\*3 and \*5), .009 (\*6), and .001 (\*7, \*15, and \*16). The defective CYP2D6 alleles \*8, \*11, \*12, \*13, and \*14 were not found. All 41 PMs (7.0%) in this sample were explained by five mutations detected by four PCR-RFLP tests, which may suffice, together with the gene duplication test, for clinical prediction of CYP2D6 capacity. Three novel variants of known CYP2D6 alleles were discovered: \*1C (T1957C), \*2B (additional C2558T), and \*4E (additional C2938T). Analysis of variance showed significant



differences in enzymatic activity measured by the dextromethorphan metabolic ratio (MR) between carriers of EM/PM (mean MR = .006) and IM/PM (mean MR = .014) alleles and between carriers of one (mean MR = .009) and two (mean MR = .003) functional alleles. The results of this study provide a solid basis for prediction of CYP2D6 capacity, as required in drug research and routine drug treatment.

Comments: Comment in: Am J Hum Genet 1997Feb;60(2):265-71

PMID: 9012401, UI: 97164594

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Pharmacogenetics 1996 Oct;6(5):395-401

A new CYP2D6 allele with a nine base insertion in exon 9 in a Japanese population associated with poor metabolizer phenotype.

Yokoi T, Kosaka Y, Chida M, Chiba K, Nakamura H, Ishizaki T, Kinoshita M, Sato K, Gonzalez FJ, Kamataki T

Division of Drug Metabolism, Faculty of Pharmaceutical Sciences, Hokkaido University, Japan.

The CYP2D6 gene of a Japanese sparteine poor metabolizer (PM, proband) showing a urinary sparteine metabolic ratio of 31.6 was analysed, and a heterozygous CYP2D6(D), a deletional type, was found by restriction fragment length polymorphism analysis with Xba I enzyme. The PM did not have any other previously described mutations in the CYP2D6 gene causing the loss of catalytic activity of the CYP2D6 enzyme. Thus, a possible new allele(s) responsible for the PM phenotype was analysed. The results indicated that the PM possessed a new 9-base insertion in exon 9, designated CYP2D6(J9). The CYP2D6(J9) and CYP2D6(D) alleles were clarified to be inherited from the mother [2D6(W)/2D6(J9)] and the father [2D6(W)/2D6(D)], respectively. The 9-base insertion caused a large increase in the apparent  $K_m$  value for bufuralolol 1'-hydroxylation as examined by expression of the enzyme protein in yeast. Four of 300 Japanese carried a heterozygous CYP2D6(J9) allele (0.7%, 4/600 chromosomes) as determined by a polymerase chain reaction analysis.

PMID: 8946471, UI: 97101953

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Pharmacogenetics 1991 Dec;1(3):143-8

Concordance of P450 2D6 (debrisoquine hydroxylase) phenotype and genotype: inability of dextromethorphan metabolic ratio to discriminate reliably heterozygous and homozygous extensive metabolizers.

Evans WE, Relling MV

Pharmaceutical Division, St. Jude Children's Research Hospital, Memphis, TN 38101.

Debrisoquine-hydroxylase (P450 2D6) not equal to phenotype was determined in 116 individuals using dextromethorphan as the substrate probe. Polymerase chain reaction and restriction fragment length polymorphism analyses were used to detect inactivating mutations in the CYP2D6 gene and assign genotype in all 116 individuals. Using a urinary metabolic ratio (DM/DT) of  $>$  or  $=$  0.3 to define poor metabolizer (PM) phenotypes, 96 subjects were extensive metabolizers (EM) and 20 were PMs. The CYP2D6(B) mutation was the most common mutation, present in 18% of phenotypic EM alleles and 66% of the alleles in PM phenotypes. The CYP2D6(A) mutation (8% of PM alleles) and the CYP2D6 gene deletion (2.6% of PM alleles) were found less frequently. Seven different variants of the CYP2D6 gene were found. In subjects with two mutant alleles, genotype correctly predicted the PM phenotype in 100% ( $n=13$ ). Overall, genotype agreed with phenotype assignments in 109 of 116 (94%) subjects. Seven subjects with a wild-type allele at the CYP2D6(A) and CYP2D6(B) loci were phenotypic PMs, representing the only discrepant results. These discrepancies could be due to the imprecision of phenotype assignment or to as yet unknown mutations in CYP2D6. Although the median urinary metabolic ratio was significantly lower in homozygous EMs compared with heterozygous EMs, there was extensive overlap in metabolic ratios in these two

groups, indicating that the DM/DT metabolic ratio cannot reliably discriminate homozygous EMS from heterozygous EMS.

PMID: 1688245, UI: 93251065

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>>> "The rate of deficiency in CYP2D6 expression in these Caucasian state psychiatric hospital patients (14%) was twice that of the U.S. population (7%)."

Am J Psychiatry 1998 Sep;155(9):1278-80

Pilot study of the cytochrome P450-2D6 genotype in a psychiatric state hospital.

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OBJECTIVE: The authors conducted a pilot study to develop preliminary data on the frequency of cytochrome P450-2D6 (CYP2D6) genotypes in state psychiatric hospital patients and to establish population sizes needed to determine potential clinical relevance in therapeutic outcome. METHOD: One hundred consecutive inpatients at Eastern State Hospital in Kentucky who provided informed consent were genotyped at the CYP2D6 locus during their hospital stay. RESULTS: Twelve of the patients were CYP2D6 deficient, and four carried the \*1Xn or \*2Xn allele associated with ultrarapid metabolism; all of these patients were Caucasian (N=87). The rate of deficiency in CYP2D6 expression in these Caucasian state psychiatric hospital patients (14%) was twice that of the U.S. population (7%). The patients with CYP2D6 deficiency also appeared more likely to experience side effects in response to CYP2D6 medications. CONCLUSIONS: This study, limited by a small number of subjects, suggests that one-fifth of Caucasians admitted to a state hospital in Kentucky had genotypes associated with extremes in CYP2D6 activity that may have affected their response to CYP2D6 medications.

PMID: 9734555, UI: 98403624

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Pharmacother 1995 May;29(5):486-8

Delirium probably induced by clarithromycin in a patient receiving fluoxetine.

Pollak PT, Sketris IS, MacKenzie SL, HewlettTU

Department of Medicine, Dalhousie University, Victoria General Hospital, Halifax, Nova Scotia, Canada.

[clarithromycin is a substrate and inhibitor of 3A,4,5,7  
norfluoxetine inhibits 3A,4,5,7  
trazodone is a substrate of 3A,4,5,7]

BACKGROUND: Clarithromycin is a macrolide antibiotic very similar to erythromycin in structure and spectrum of activity. It has gained increasing use since its release in Canada in May 1992, partly because it is promoted as having less potential for drug interactions and adverse effects. However, as with all new medications, a high degree of vigilance for unreported adverse effects is advisable. CASE SUMMARY: A healthy 53-year-old lawyer was receiving long-term fluoxetine 80 mg hs and nitrazepam 10 mg hs for depression and mild sleep apnea. Subsequent to initiation of treatment with clarithromycin for a respiratory infection, he rapidly developed delirium, which cleared quickly after stopping all 3 medications. The delirium and psychosis did not recur when the infection was treated with erythromycin alone or after restarting fluoxetine and nitrazepam therapy at previous dosages in the absence of antibiotics. DISCUSSION: This man's delirium is consistent with fluoxetine intoxication, which appears to have resulted from inhibition of hepatic cytochrome P450 metabolism by clarithromycin. Undiagnosed, this serious drug reaction could have led to serious medical and social consequences. CONCLUSIONS: As the use of clarithromycin increases,

the potential for interactions with other drugs metabolized by the P450 enzyme system may be realized. Clinicians should consider which other medications a patient is receiving before prescribing clarithromycin or any macrolide antibiotic with potential to influence the P450 system.

Comments: Comment in: Ann Pharmacother 1996Oct;30(10):1199-200

PMID: 7655131, UI: 95383785

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J Clin Psychiatry 1998;59 Suppl 10:22-6

Pharmacokinetic interactions of antidepressants.

Richelson E

Department of Psychiatry and Pharmacology, Mayo Medical School, Rochester, Minn, USA.

Seven of the newest antidepressants are the serotonin selective reuptake inhibitors (fluoxetine, sertraline, paroxetine, and fluvoxamine [currently approved in the United States for obsessive-compulsive disorder only]), a serotonin norepinephrine reuptake inhibitor (venlafaxine), a postsynaptic serotonin antagonist/presynaptic serotonin reuptake inhibitor (nefazodone), and presynaptic/postsynaptic noradrenergic/serotonergic receptor antagonist (mirtazapine). Many of these drugs are potent inhibitors of the cytochrome P450 (CYP) enzymes of the liver. The CYP enzymes most relevant to the use of antidepressants and for which the most thorough data are available are the CYP1A2, CYP2D6, and CYP3A4. These 3 CYP isoenzymes are discussed in relation to some of the drugs they metabolize, and appropriate cautions are recommended for concurrent administration of these new antidepressants and other drugs frequently prescribed to elderly patients.

Publication Types: Review Review, tutorial

PMID: 9720479, UI: 98385433

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Ann Clin Psychiatry 1993 Dec;5(4):255-7

Delirium during fluoxetine treatment. A case report.

Leinonen E, Koponen H, Lepola U

Psychiatric Research Clinic of Kuopio, Finland.

The correlation between high serum tricyclic antidepressant concentrations and central nervous system side effects has been well established. Only a few reports exist, however, on the relationship between the serum concentrations of selective serotonin reuptake inhibitors (SSRIs) and their toxic effects. In some cases, a high serum concentration of citalopram (> 600 nmol/L) in elderly patients has been associated with increased somnolence and movement difficulties. Widespread cognitive disorders, such as delirium, have not been previously linked with high blood levels of SSRIs. In this report, we describe a patient with acute hyperkinetic delirium connected with a high serum total fluoxetine (fluoxetine plus desmethylfluoxetine) concentration.

PMID: 8312983, UI: 94146884

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J Med Assoc Thai 1995 Jan;78(1):53-4

Reversible delirium after discontinuation of fluoxetine.

Kasantikul D

Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

An elderly patient developed confusion, disorientation and visual hallucination twice following discontinuation of fluoxetine. The mental symptoms, however, disappeared after ingestion of this antidepressant drug. Such an apparent withdrawal complication of fluoxetine has not been reported previously.

PMID: 7622979, UI: 95348641

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Psychosomatics 1992 Spring;33(2):224-6

Fluoxetine and organic mood syndrome.

Bessette RF, Peterson LG

Department of Psychiatry, University of Massachusetts Medical Center, Worcester 01605.

PMID: 1557490, UI: 92213169

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Am J Psychiatry 1990 Apr;147(4):532

Serious adverse effects of combining fluoxetine and tricyclic antidepressants.

Preskorn SH, Beber JH, Faul JC, Hirschfeld RM

Publication Types: Letter

PMID: 2107764, UI: 90196392

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Br J Clin Pharmacol 1997 Sep;44(3):303-4

A genetic bias in clinical trials? Cytochrome P450-2D6 (CYP2D6) genotype in general vs selected healthy subject populations.

Chen S, Kumar S, Chou WH, Barrett JS, Wedlund PJ

Publication Types: Letter

PMID: 9296329, UI: 97442111

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J Clin Psychopharmacol 1997 Oct;17(5):358-64

Effects of trazodone and fluoxetine in the treatment of major depression: therapeutic pharmacokinetic and pharmacodynamic interactions through formation of meta-chlorophenylpiperazine.

Maes M, Westenberg H, Vandoolaeghe E, Demedts P, Wauters A, Neels H, Meltzer HY

Clinical Research Center for Mental Health (CRC-MH), University Department of Psychiatry, Antwerp, Belgium.

It has been suggested that (1) the clinical efficacy of the heterocyclic antidepressant trazodone in depression may, in part, be attributed to its metabolite meta-chlorophenylpiperazine (mCPP); and (2) the enhancement of the efficacy of trazodone by the addition of fluoxetine, a selective serotonin reuptake inhibitor,

may, in part, be ascribed to fluoxetine-induced plasma concentrations of trazodone. After a washout period of 10 days, 27 inpatients with major depression were treated with trazodone 100 mg/day (orally). One week later (T0), fluoxetine 20 mg/day, placebo, or pindolol 7.5 mg/day was added. Plasma concentrations of mCPP and trazodone were determined at T0 and 2 and 4 weeks later. Although placebo pindolol had no significant effect on the plasma concentrations of mCPP and trazodone, there was a significant increase of the concentrations of these compounds associated with the combination of trazodone + fluoxetine. The results suggest that fluoxetine-induced increases in plasma mCPP and trazodone concentrations contribute to the clinical efficacy of the combination of fluoxetine + trazodone. It is suggested that desensitization of 5-HT<sub>2C</sub> receptor function by mCPP as well as fluoxetine may contribute to the antidepressant effects of this combination.

Publication Types: Clinical trial Randomized controlled trial

PMID: 9315986, UI: 97461711

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>>> "fluoxetine and norfluoxetine are potent inhibitors of CYP2D6... This can give rise to drug-drug interactions that may have no effect, lead to intoxication, or improve the therapeutic response"

Pharmacol Ther 2000 Jan;85(1):11-28

Pharmacokinetics of selective serotonin reuptake inhibitors.

Hiemke C, Hartter S

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The five selective serotonin reuptake inhibitors (SSRIs), fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram, have similar antidepressant efficacy and a similar side effect profile. They differ, however, in their pharmacokinetic properties. Under steady-state concentrations, their half-lives range between 1 and 4 days for fluoxetine (7 and 15 days for norfluoxetine) and between 21 (paroxetine) and 36 (citalopram) hr for the other SSRIs. Sertraline and citalopram show linear and fluoxetine, fluvoxamine, and paroxetine nonlinear pharmacokinetics. SSRIs underlie an extensive metabolism with high inter individual variability, whereby cytochrome P450 (CYP) isoenzymes play a major role. Therefore, resulting blood concentrations are highly variable between individuals. Except for N-demethylated fluoxetine, metabolites of SSRIs do not contribute to clinical actions. Therapeutically effective blood concentrations are unclear so far, although there is evidence for minimal effective and upper-threshold concentrations that should not be exceeded. Paroxetine and, to a lesser degree, fluoxetine and norfluoxetine are potent inhibitors of CYP2D6 and fluvoxamine of CYP1A2 and CYP2C19. This can give rise to drug-drug interactions that may have no effect, lead to intoxication, or improve the therapeutic response. These different pharmacokinetic properties of the five SSRIs, especially their drug-drug interaction potential, should be considered when selecting a distinct SSRI for treatment of depression or other disorders with a suggested dysfunction of the serotonergic system in the brain.

Publication Types: Review Review, academic

PMID: 10674711, UI: 20137176

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>>> "SSRIs are potent inhibitors of the hepatic isoenzyme P450-2D6 and would be expected to have effects on the clearance of drugs metabolized by this enzyme."

Encephale 1999 Sep-Oct;25(5):470-6

[Pharmacokinetics of SSRI antidepressants: half-life and clinical applicability].

[Article in French]

Gury C, Cousin F

Pharmacien des Hopitaux, CH Sainte-Anne, Paris.

The selective serotonin reuptake inhibitors (SSRIs) antidepressants are at present time the most useful for the treatment of depression. SSRIs exhibit differences in potency of inhibiting serotonin reuptake, although the differences do not correlate with clinical efficacy. There are substantial pharmacokinetic differences among the five SSRIs, fluvoxamine, fluoxetine, paroxetine, sertraline and citalopram. Optimum use of these drugs requires a working knowledge of these differences. Among these pharmacokinetic parameters, half-life and metabolism pathways are the most relevant. There are substantial differences in terms of their half-life between fluoxetine and others SSRIs. The half-life of fluoxetine and its active metabolite norfluoxetine is respectively 2 to 4 days and 7 to 15 days, more extended than other SSRIs (approximately 1 day). The extended half-life of fluoxetine and its active metabolite may be an advantage in the poorly compliant patient and may offer a potential safety advantage over shorter-acting SSRIs, with respect to abrupt discontinuation of therapy. Conversely, this long half-life needs a long period of wash-out (5 weeks) before introducing other drugs (MAOIs, sumatriptan) which can interact with serotonin function and can lead to the serotoninergic syndrome. SSRIs are potent inhibitors of the hepatic isoenzyme P450-2D6 and would be expected to have effects on the clearance of drugs metabolized by this enzyme. Paroxetine is the most potent inhibitor, followed by fluoxetine, sertraline, citalopram and fluvoxamine. The metabolite elimination of citalopram, paroxetine and fluvoxamine is delayed by renal disease and dosages should be lowered in elderly patients. Conversely the pharmacokinetic of fluoxetine and sertraline are not affected by either age or renal impairment and, for fluoxetine, by obesity.

Publication Types: Review Review, tutorial

PMID: 10598311, UI: 20066258

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>>> "CYP2D6 is inhibited by SSRIs, in order of decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram and fluvoxamine. This may have clinical consequences with some but not all SSRIs, when they are taken with tricyclic antidepressants.... There have been many reports on marked pharmacokinetic interactions between fluoxetine and tricyclic antidepressants."

Clin Pharmacokinet 1996 Dec;31(6):444-69

Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors.

Baumann P

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The recently introduced antidepressants, the selective serotonin reuptake inhibitors (SSRIs) [citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline], are known for their clinical efficacy, good tolerability and relative safety. They differ from each other in chemical structure, metabolism and pharmacokinetic properties. Therapeutic drug monitoring of these compounds is not widely used, as the plasma concentration ranges within which clinical response with minimal adverse effects appears to be optimal are not clearly defined. Almost all recent assays developed for the quantitative determination of SSRIs and their metabolites in blood are based either on the separation of SSRIs by high performance liquid chromatography (HPLC) or gas chromatography (GC). Citalopram and fluoxetine have been introduced as racemic compounds. There are some differences in the pharmacological profile, metabolism and pharmacokinetics between the enantiomers of the parent compounds and their demethylated metabolites. Stereoselective chromatographic methods for their analysis in blood are now available. With regard to the SSRIs presently available, no clearcut plasma concentration-clinical effectiveness relationship in patients with depression has been shown, nor any threshold which defines toxic concentrations. This may be explained by their low toxicity and use at dosages where serious adverse effects do not appear. SSRIs vary widely in their qualitative and quantitative interaction with cytochrome P450 (CYP) isozymes in the liver. CYP2D6 is inhibited by SSRIs, in order of

decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline, citalopram and fluvoxamine. This may have clinical consequences with some but not all SSRIs, when they are taken with tricyclic antidepressants. Except for citalopram and paroxetine, little is known about the enzymes which control the biotransformation of the SSRIs. There have been many reports on marked pharmacokinetic interactions between fluoxetine and tricyclic antidepressants. Fluoxetine has a stronger effect on their hydroxylation than on their demethylation. Interactions observed between fluoxetine and alprazolam, midazolam and carbamazepine seem to occur on the level of CYP3A. Fluvoxamine strongly inhibits the N-demethylation of some tricyclic antidepressants of the tertiary amine type and of clozapine. This may lead to adverse effects but augmentation with fluvoxamine can also improve response in very rapid metabolisers, as it increases the bioavailability of the comedication. Fluvoxamine inhibits with decreasing potency, CYP1A2, CYP2C19, CYP2D6 and CYP1A1, but it is also an inhibitor of CYP3A. Fluoxetine and fluvoxamine have shown to increase methadone plasma concentrations independent patients. Some authors warn about a combination of monoamine oxidase (MAO) inhibitors with SSRIs, as this could lead to a serotonergic syndrome. Studies with healthy volunteers suggest, however, that a combination of moclobemide and SSRIs, such as fluvoxamine, should not present serious risks in promoting a serotonin syndrome. A combination of moclobemide and fluvoxamine has successfully been used in refractory depression, but more studies are needed, including plasma-concentration monitoring, before this combined treatment can be recommended. Paroxetine is a substrate of CYP2D6, but other enzyme(s) could also be involved. Its pharmacokinetics are linear in poor metabolisers of sparteine, and non-linear in extensive metabolisers. Due to its potent CYP2D6 inhibiting properties, comedication with this SSRI can lead to an increase of tricyclic antidepressants in plasma, as shown with amitriptyline and trimipramine. CYP3A has been claimed to be involved in the biotransformation of sertraline to norsertraline. Clinical investigations (with desipramine) confirmed in vitro findings that CYP2D6 inhibition by sertraline is only moderate.

Publication Types: Review Review, tutorial

PMID: 8968657, UI: 97123410

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>>> "norfluoxetine is more potent than fluoxetine as an inhibitor of CYP3A3/4, and in view of the longer half-life( $t_{1/2}$ ) of the metabolite the potential for interactions may persist for weeks after discontinuation of the parent drug"

Clin Pharmacokinet 1998 Apr;34(4):281-302

Metabolism of the newer antidepressants. An overview of the pharmacological and pharmacokinetic implications.

Caccia S

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Several chemically unrelated agents has been developed and introduced in the past decade, to supplement the earlier antidepressants. These include inhibitors of the reuptake of serotonin [the selective serotonin reuptake inhibitors (SSRI)] or noradrenaline (reboxetine) or both (milnacipran and venlafaxine), as well as drugs with distinct neurochemical profiles such as mirtazapine, nefazodone, moclobemide and tianeptine. Like the earlier drugs, these newer antidepressants are almost totally biotransformed before excretion, except for milnacipran whose clearance appears to be due equally to both urinary excretion and metabolism. Sometimes--as in the case of moclobemide--up to 20 metabolites have been identified in body fluids. In some cases, however, only a few metabolites have been detected, and a substantial proportion of the dose remains unaccounted for (e.g. fluoxetine and fluvoxamine). Metabolism generally proceeds through sequential or parallel oxidative pathways. These may be affected to varying degrees by physiological and pathological factors and those mediated by cytochrome P450 (CYP) 2D6 and CYP2C19 through genetic polymorphism. Some are influenced by chirality (e.g. the dealkylation of citalopram and fluoxetine), although information on this aspect of disposition is still lacking for other drugs existing as racemates (e.g. mirtazapine and tianeptine) and milnacipran, which is probably a mixture of 4 stereoisomers. Others again are saturable within the therapeutic range of doses (e.g. some pathways of metabolism of fluoxetine, fluvoxamine, nefazodone, paroxetine and venlafaxine). This may explain the individual variability with all these drugs which, from the pharmacokinetic point of view, is the

same as with tricyclic agents. Our knowledge of the isoenzymes involved in the various oxidation pathways and their relevance for potential drug interactions varies from a considerable amount for most of the SSRI and nefazodone, to minimal for reboxetine and tianeptine. This information is useful for predicting the pharmacokinetic interactions mediated through inhibition of specific isoenzymes. This would be better appreciated if the enzymatic mechanisms involved in the biotransformation of the metabolite(s), and their role in drug interactions, were also known. This information is still lacking for some drugs, although metabolites may exhibit in vitro inhibitory potencies of similar to (paroxetine and its M2 metabolite as inhibitors of CYP2D6) or even greater than that of the parent drug (norfluoxetine is more potent than fluoxetine as an inhibitor of CYP3A3/4, and in view of the longer half-life ( $t_{1/2}$ ) of the metabolite the potential for interactions may persist for weeks after discontinuation of the parent drug). While we do know something about the biological activity of the metabolites of some of these drugs, we know very little about others. With few exceptions this knowledge refers only to the major metabolite(s) and regards the main in vitro effects as exerted by the parent drug. However, in vitro potency and selectivity may not translate directly into in vivo, and either major or minor metabolites may have characteristic in vitro and in vivo properties. For example, unlike the parent drug some minor ring-opened metabolites of moclobemide have monoamine oxidase-B inhibitory activity in the rat, and the nefazodone metabolite m-chlorophenyl-piperazine shows activity on 5-HT<sub>2C</sub> receptors in rats and humans. Data on the brain-to-blood partition of metabolites compared with their parent drug are available only in a few cases. They are still not known for the main metabolites of fluvoxamine, milnacipran, mirtazapine, moclobemide, nefazodone, paroxetine, reboxetine and venlafaxine, despite the fact that total blood concentrations do not always reflect the metabolite: parent drug ratio in brain. Thus, in most cases, we do not really know what part hepatic metabolism plays in the overall effect of the administered parent drug.

Publication Types: Review Review, tutorial

PMID: 9571301, UI: 98232792

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Fundam Clin Pharmacol 1998;12(2):194-9

In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine.

Iribarne C, Picart D, Dreano Y, Berthou F

Laboratoires de Biochimie Nutrition EA-948, Faculte de Medecine, Brest, France.

Methadone and buprenorphine, widely used in the treatment of opioid abuse, are metabolized by cytochrome P450 3A4, while fluoxetine and fluvoxamine, both selective serotonin reuptake inhibitors, are known to be P450 2D6 and 3A4 inhibitors in vitro. This study deals with the in vitro interactions between methadone or buprenorphine and fluoxetine or fluvoxamine. Fluoxetine inhibited methadone N-demethylation ( $K_i = 55$  microM), but conversely did not inhibit buprenorphine dealkylation. Norfluoxetine inhibited the metabolism of both methadone and buprenorphine metabolisms ( $K_i$  13 and 100 microM, respectively). Fluvoxamine inhibited methadone N-demethylation with a  $K_i$  of 7 microM and buprenorphine dealkylation, uncompetitively, with a  $K_i$  of 260 microM. Finally, these results suggest that care should be taken when selective serotonin reuptake inhibitors are administered in the treatment of drug craving. This is particularly true in the case of fluvoxamine which is more potent than fluoxetine in inhibiting methadone and buprenorphine metabolism.

PMID: 9565774, UI: 98226895

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>>> "fluoxetine, largely via its metabolite norfluoxetine, may impair clearance of P450-3A substrates"

J Clin Pharmacol 1996 Sep;36(9):783-91

Midazolam hydroxylation by human liver microsomes in vitro: inhibition by fluoxetine, norfluoxetine, and by azole antifungal agents.



von Moltke LL, Greenblatt DJ, Schmider J, Duan SX, Wright CE, Harmatz JS, Shader RI

Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111, USA.

Biotransformation of the imidazobenzodiazepine midazolam to its alpha-hydroxy and 4-hydroxy metabolites was studied in vitro using human liver microsomal preparations. Formation of alpha-hydroxy-midazolam was a high-affinity ( $K_m = 3.3 \mu\text{mol/L}$ ) Michaelis-Menten process coupled with substrate inhibition at high concentrations of midazolam. Formation of 4-hydroxy-midazolam had much lower apparent affinity ( $57 \mu\text{mol/L}$ ), with minimal evidence of substrate inhibition. Based on comparison of  $V_{\text{max}}/K_m$  ratios for the two pathways, alpha-hydroxy-midazolam formation was estimated to account for 95% of net intrinsic clearance. Threeazole antifungal agents were inhibitors of midazolam metabolism in vitro, with inhibition being largely consistent with a competitive mechanism. Mean competitive inhibition constants ( $K_i$ ) versus alpha-hydroxy-midazolam formation were  $0.0037 \mu\text{mol/L}$  for ketoconazole,  $0.27 \mu\text{mol/L}$  for itraconazole, and  $1.27 \mu\text{mol/L}$  for fluconazole. An in vitro-in vivo scaling model predicted inhibition of oral midazolam clearance due to coadministration of ketoconazole or itraconazole; the predicted inhibition was consistent with observed interactions in clinical pharmacokinetic studies. The selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine and its principal metabolite, norfluoxetine, also were inhibitors of both pathways of midazolam biotransformation, with norfluoxetine being a much more potent inhibitor than was fluoxetine itself. This finding is consistent with results of other in vitro studies and of clinical studies, indicating that fluoxetine, largely via its metabolite norfluoxetine, may impair clearance of P450-3A substrates.

PMID: 8889898, UI: 97044827

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>>> "norfluoxetine was the only potent inhibitor of CYP3A"

Br J Clin Pharmacol 1995 Feb;39(2):151-9

Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine.

Rasmussen BB, Maenpaa J, Pelkonen O, Loft S, Poulsen HE, Lykkesfeldt J, Brosen K

Department of Clinical Pharmacology, Odense University, Denmark.

1. Fluvoxamine and seven other selective serotonin reuptake inhibitors (SSRI) were tested for their ability to inhibit a number of human cytochrome P450 isoforms (CYPs). 2. None of the drugs showed potent inhibition of CYP2A6 (coumarin 7-hydroxylase) or CYP2E1 (chlorzoxazone 6-hydroxylase), while norfluoxetine was the only potent inhibitor of CYP3A having  $IC_{50}$  values of  $11 \mu\text{M}$  and  $19 \mu\text{M}$  for testosterone 6 beta-hydroxylase and cortisol 6 beta-hydroxylase, respectively. 3. Norfluoxetine, sertraline and fluvoxamine inhibited CYP1A1 (7-ethoxyresorufin O-deethylase) in microsomes from human placenta ( $IC_{50}$  values  $29 \mu\text{M}$ ,  $35 \mu\text{M}$  and  $80 \mu\text{M}$ , respectively). Fluvoxamine was a potent inhibitor of CYP1A2-mediated 7-ethoxyresorufin O-deethylase activity ( $IC_{50} = 0.3 \mu\text{M}$ ) in human liver. 4. In microsomes from three human livers fluvoxamine potently inhibited all pathways of theophylline biotransformation, the apparent inhibitor constant,  $K_i$ , was  $0.07-0.13 \mu\text{M}$ ,  $0.05-0.10 \mu\text{M}$  and  $0.16-0.29 \mu\text{M}$  for inhibition of 1-methylxanthine, 3-methylxanthine and 1,3-dimethyluric acid formation, respectively. Seven other SSRIs showed either weak or no inhibition of theophylline metabolism. 5. Ethanol inhibited the formation of 1,3-dimethyluric acid with  $K(i)$  value of  $300 \mu\text{M}$ , a value which is consistent with inhibition of CYP2E1. Ethanol and fluvoxamine both inhibited 8-hydroxylation by about 45% and, in combination, the compounds decreased the formation of 1,3-dimethyluric acid by 90%, indicating that CYP1A2 and CYP2E1 are equally important isoforms for the 8-hydroxylation of theophylline. 6. It is concluded that pharmacokinetic interaction between fluvoxamine and theophylline is due to potent inhibition of CYP1A2.

PMID: 7742153, UI: 95260648

>>> Lilly reports "fluoxetine and norfluoxetine together would inhibit CYP3A catalytic activity by less than 7%" -- [DISAGREES WITH OTHER RESULTS]

J Pharmacol Exp Ther 1995Dec;275(3):1131-5

Effect of fluoxetine, norfluoxetine, sertraline and desmethyl sertraline on human CYP3A catalyzed 1'-hydroxymidazolam formation in vitro.

Ring BJ, Binkley SN, Roskos L, Wrighton SA

Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.

The ability of fluoxetine, norfluoxetine, sertraline and desmethyl sertraline to inhibit the CYP3A subfamily of cytochromes P450 was examined in vitro, using the formation of 1'-hydroxymidazolam as a probe for CYP3A catalytic activity. The inhibition observed with these four compounds was modeled using competitive, noncompetitive, uncompetitive and mixed competitive/noncompetitive relationships by nonlinear regression analysis. The best fit model of the inhibition of CYP3A-mediated 1'-hydroxymidazolam formation by all four compounds examined was determined to be mixed inhibition. The calculated  $K_i$  values were 65.7  $\pm$  12.0  $\mu\text{M}$  for fluoxetine, 19.1  $\pm$  1.9  $\mu\text{M}$  for norfluoxetine, 64.4  $\pm$  11.6  $\mu\text{M}$  for sertraline and 48.1  $\pm$  11.6  $\mu\text{M}$  for desmethyl sertraline. Steady-state plasma levels of fluoxetine and norfluoxetine can approach a concentration of 1  $\mu\text{M}$  (approximately 350 ng/ml of plasma). Assuming an inhibitor concentration of 1  $\mu\text{M}$  and a concentration of the substrate substantially below its  $K_m$  (at least 10-fold lower), the results reported predict that fluoxetine and norfluoxetine together would inhibit CYP3A catalytic activity by less than 7% (less than 0.7% if the unbound plasma concentration of fluoxetine is considered). By using the same assumptions and concentrations for sertraline and desmethyl sertraline, these agents together would be predicted to inhibit the metabolic clearance of a coadministered CYP3A metabolized drug by less than 4%. The observations reported here suggest that fluoxetine and sertraline would have little effect on CYP3A-mediated clearance of coadministered drugs.

PMID: 8531073, UI: 96108599

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>>> Fluoxetine -> Cytochrome P450-2C9 -> Norfluoxetine

Psychopharmacology (Berl) 1997Aug;132(4):402-7

Human cytochromes mediating N-demethylation of fluoxetine in vitro.

von Moltke LL, Greenblatt DJ, Duan SX, Schmider J, Wright CE, Harmatz JS, Shader RI

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Biotransformation of the selective serotonin reuptake inhibitor antidepressant, fluoxetine, to its principal metabolite, norfluoxetine, was evaluated in human liver microsomes and in microsomes from transfected cell lines expressing pure human cytochromes. In human liver microsomes, formation of norfluoxetine from R,S-fluoxetine was consistent with Michaelis-Menten kinetics (mean  $K_m$  = 33  $\mu\text{M}$ ), with evidence of substrate inhibition at high substrate concentrations in a number of cases. The reaction was minimally inhibited by coincubation with chemical probes inhibitory for P450-2D6 (quinidine), -1A2 (furafylline,  $\alpha$ -naphthoflavone), and -2E1 (diethyldithiocarbamate). Substantial inhibition was produced by coincubation with sulfaphenazole ( $K_i$  = 2.8  $\mu\text{M}$ ), an inhibitory probe for P450-2C9, and by ketoconazole ( $K_i$  = 2.5  $\mu\text{M}$ ) and fluvoxamine ( $K_i$  = 5.2  $\mu\text{M}$ ). However, ketoconazole, relatively specific for P450-3A isoforms only at low concentrations, reduced norfluoxetine formation by only 20% at 1  $\mu\text{M}$ , and triacetyloleandomycin ( $>$  or = 5  $\mu\text{M}$ ) reduced the velocity by only 20-25%. Microsomes from cDNA-transfected human lymphoblastoid cells containing human P450-2C9 produced substantial quantities of norfluoxetine when incubated with 100  $\mu\text{M}$  fluoxetine. Smaller amounts of product were produced by P450-2C19 and -2D6, but no product was produced by P450-1A2, -2E1, or 3A4. Cytochrome P450-2C9 appears to be the principal human cytochrome mediating fluoxetine N-demethylation.

P450-2C19 and -3A may make a further small contribution, but P450-2D6 is unlikely to make an important contribution.

PMID: 9298519, UI: 97443743

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Br J Clin Pharmacol 1997 Nov;44(5):495-8

Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation.

Schmider J, Greenblatt DJ, von Moltke LL, Karsov D, Shader RI

Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111, USA.

AIMS: Inhibition of cytochrome P450 (CYP) activity by selective serotonin reuptake inhibitors (SSRIs) has frequently been reported with regard to pathways mediated by CYP2D6, CYP3A4/5, and CYP1A2. Little data exist on the capability of SSRIs to inhibit CYP2C9. METHODS: We investigated the effect of SSRIs on p-hydroxylation of phenytoin (PPH), an established index reaction reflecting CYP2C9 activity, in an in vitro assay using liver tissue from six different human donors. RESULTS: In control incubations (without inhibitor), 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH) formation rates were:  $V_{max} 0.023 \text{ nmol min}^{-1} \text{ mg}^{-1}$ ;  $K_m 14.3 \text{ microM}$ . Average inhibition constants ( $K_i$ ) differed significantly among the SSRIs, with fluvoxamine having the lowest  $K_i$  (6 microM) followed by R-fluoxetine (13 microM), norfluoxetine (17 microM), RS-fluoxetine (19 microM), sertraline (33 microM), paroxetine (35 microM), S-fluoxetine (62 microM), and desmethyl sertraline (66 microM). Thus, assuming comparable molar concentrations at the site of inhibition, fluvoxamine can be expected to have the highest probability of interfering with the metabolism of CYP2C9 substrates. S-fluoxetine is on average a 5 fold weaker CYP2C9 inhibitor than either R-fluoxetine or the racemic mixture. CONCLUSIONS: These findings are consistent with published case reports describing SSRI-related increments in plasma phenytoin levels. Because phenytoin has a narrow therapeutic index, plasma levels should be closely monitored when SSRIs are coadministered.

PMID: 9384467, UI: 98044123

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<http://www.ionet.net/~jcott/homepage/drugdb/062.html>

DRUG INTERACTIONS: Fluoxetine potentiates serotonin by inhibiting its neuronal reuptake. Since serotonin is deaminated by monoamine oxidase type A, administration of drugs that can inhibit this enzyme concurrently with fluoxetine can lead to a serious reaction known as "serotonin syndrome." This reaction may include confusion, seizures, and severe hypertension as well as less severe symptoms. Most MAOIs are non-specific inhibitors of MAO (e.g., furazolidone, pargyline, phenelzine, tranylcypromine) and, since they affect MAO type A, should not be used with fluoxetine. In addition, selegiline, although selective for MAO type B at usual doses, may inhibit MAO type A at higher doses and should also be avoided in patients receiving fluoxetine. Finally, procarbazine, an antineoplastic agent, is a weak MAOI and should also be avoided. At least 2 weeks should elapse between the discontinuation of MAOI therapy and the start of fluoxetine therapy, and at least 5 weeks between the discontinuation of fluoxetine therapy and commencement of MAOI therapy. This 5-week period is needed because of the long half-life of fluoxetine and its principal metabolite norfluoxetine.

Fluoxetine impairs metabolism of the CYP2D6 (cytochrome P-450 isoenzyme 2D6) pathway at therapeutic doses. This can cause substantial increases in concentrations of other drugs metabolized via the same pathway. Plasma concentrations of tricyclic antidepressants, maprotiline, and trazodone can double when used concomitantly with fluoxetine. Concomitant use of trazodone with fluoxetine can lead to excessive sedation and unstable gait. When tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, desipramine) have been used concomitantly with fluoxetine, symptoms of tricyclic toxicity (such as sedation, decreased energy, lightheadedness, psychomotor retardation, xerostomia, constipation, and memory impairment) have been reported. The clinical need for antidepressant polypharmacy is unknown and should be undertaken only after careful consideration of alternatives and with careful

monitoring.

Fluoxetine impairs metabolism of the CYP2D6 (cytochrome P-450 isozyme 2D6) pathway at therapeutic doses. This can result in substantial increases in concentrations of other drugs metabolized via the same pathway. Fluoxetine may prolong the half-life of diazepam, but the psychomotor and physiological response does not appear to be altered. Fluoxetine has also been reported to affect the clearance and plasma concentrations of alprazolam, but had no effect on clonazepam or triazolam.

Fluoxetine impairs metabolism of the CYP2D6 (cytochrome P-450 isozyme 2D6) pathway at therapeutic doses. This can result in substantial increases in concentrations of other drugs metabolized via the same pathway. Fluoxetine may increase the risk of adverse effects of haloperidol, loxapine, molindone, phenothiazines, phenytoin, pimozide, or thiothixene if administered with any of these agents. Serum clozapine concentrations increased substantially when fluoxetine was coadministered. The effects of fluoxetine on hepatic metabolism may persist after discontinuation of fluoxetine because of its long elimination half-life.

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From the RxList Prozac monograph

#### DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms (eg, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY).

Drugs Metabolized by P450IID6 (2d6)--Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs s.c. as debrisoquin, dextromethorphan, and tricyclic antidepressants. Many drugs, s.c. as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in p.o. metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the 4 active enantiomers is comparable between p.o. and extensive metabolizers (see Variability in Metabolism under CLINICAL PHARMACOLOGY).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (see list below), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/ her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (eg, flecainide, vinblastine, and tricyclic antidepressants).

Drugs Metabolized by Cytochrome P450IIIA4(3a4)-- In an in vivo interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P450IIIA4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of cytochrome P450IIIA4 activity is not likely to be of clinical significance.

CNS Active Drugs-- The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and s.c. drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY).

Monoamine Oxidase Inhibitors-- see CONTRAINDICATIONS.

Other Antidepressants-- In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10- fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see Accumulation and Slow Elimination under CLINICAL PHARMACOLOGY, and Drugs Metabolized by P450IID6 under DRUG INTERACTIONS).