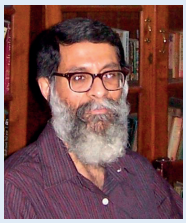
Augmenting Selective Serotonin Reuptake Inhibitors With Clomipramine in Obsessive-Compulsive Disorder: Benefits and Risks

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

A small body of literature suggests that clomipramine may usefully augment selective serotonin reuptake inhibitor (SSRI) treatment in obsessive-compulsive disorder (OCD) patients who do not respond to SSRI monotherapy. The combination, however, is associated with the risk of clinically significant drug interactions. Clomipramine can raise the blood levels and hence the adverse effects of most SSRIs, and many SSRIs can raise the blood levels and hence the adverse effects of clomipramine. The latter situation is more important because certain dose-dependent adverse effects of clomipramine, such as seizures, can be life-threatening. This article presents an evidence-based discussion of the pharmacodynamic and pharmacokinetic adverse effects of the SSRI-clomipramine combination along with suggestions for dosing and monitoring when the combination is used in OCD.

J Clin Psychiatry 2013;74(12):e1128–e1133 (doi:10.4088/JCP.13f08883)

Clinical Problem

A 16-year-old boy was prescribed fluoxetine for obsessive-compulsive disorder (OCD). The dose was stepped up from 20 mg/d to 60 mg/d across 4 weeks. Despite adequate drug compliance, there was only modest improvement, and, therefore, clomipramine (25 mg/d) was added 3 months later to augment the fluoxetine-mediated benefits. Encouraging results led to a stepwise increase in the dose of clomipramine from 25 mg/d to 75 mg/d. What might be the risks associated with the combination of fluoxetine (60 mg/d) with clomipramine (75 mg/d)?

Why Augment an SSRI With Clomipramine?

Clomipramine is generally acknowledged to be the most effective monotherapy for OCD; for example, a meta-regression analysis of 12 randomized controlled trials (RCTs) in pediatric OCD[1] found that clomipramine was superior to the selective serotonin reuptake inhibitors (SSRIs), which did not differ significantly among themselves. However, clomipramine is associated with significant anticholinergic and other adverse effects,[2] and so SSRIs tend to be chosen as first-line agents for patients with OCD.[3] In such situations, the dose of the SSRI is usually stepped up, depending on how well the drug is tolerated, because higher doses are associated with greater anti-OCD efficacy.[4]

Unfortunately, patients with OCD do not always respond adequately to initial treatment with an SSRI,[5] and augmentation strategies therefore become necessary. Whereas drugs such as buspirone, clonazepam, and others have been used for SSRI augmentation, the largest body of evidence supports augmentation with atypical antipsychotic drugs.[6–8]

Among the atypical antipsychotics, a recent meta-analysis[8] of 12 RCTs found that risperidone (3 RCTs) was associated with the best evidence of benefit; neither quetiapine (5 RCTs) nor olanzapine (2 RCTs) was associated with significant efficacy, and the benefits with aripiprazole and haloperidol (1 RCT each) were inconsistent. A problem with risperidone is that it can cause adverse effects such as weight gain, extrapyramidal symptoms, and prolactin elevation.[9] Some clinicians therefore offer an SSRI-clomipramine trial before augmenting SSRIs with an atypical antipsychotic drug. Usually in such trials, the SSRI drug is prescribed in its full therapeutic dose, and clomipramine is prescribed in a low dose. The expectation is that the serotonergic effect of the combination will be greater than that with SSRI monotherapy and that clomipramine will be reasonably well tolerated because the dose is low.

Benefits of the SSRI-Clomipramine Combination

There is anecdotal as well as RCT-based evidence for anti-OCD benefits with an SSRI-clomipramine combination. For example, Simeon et al[10] reported the use of a fluoxetine-clomipramine combination in 6 adolescents with OCD, all of whom had failed to tolerate or respond to clomipramine monotherapy. Combination treatment duration ranged from 4 to 28 weeks and beyond; doses were 20–40 mg/d for fluoxetine and 25–50 mg/d for clomipramine. All patients responded better to the combination than to clomipramine monotherapy. Furthermore,

- Clomipramine augmentation of SSRIs may improve treatment response in obsessive-compulsive disorder patients in whom response to SSRI monotherapy is inadequate.
- Clomipramine can raise the blood levels and hence the adverse effects of most SSRIs. More importantly, fluoxetine, fluvoxamine, and possibly high doses of the other SSRIs can raise the blood levels and hence the adverse effects of clomipramine, resulting in treatment-limiting adverse effects, as well as life-threatening problems such as QTc prolongation and seizures.
- When combining fluoxetine or fluvoxamine with clomipramine, it is best to use low doses of each drug. In particular, doses of clomipramine should not exceed 75 mg/d unless the blood clomipramine level is monitored. Electrocardiographic monitoring of the QTc interval is also desirable.

combination therapy was better tolerated than clomipramine monotherapy. Browne et al[11] described 4 patients with severe OCD; 2 improved with the fluoxetine-clomipramine combination after failing trials with these drugs in monotherapy. The other 2 showed further improvement when fluoxetine was added to clomipramine therapy. Doses were 20–60 mg/d for fluoxetine and 50–250 mg/d for clomipramine. Figueroa et al[12] reported 7 patients who were effectively treated with a combination of clomipramine and fluvoxamine, paroxetine, or sertraline.

In an open-label comparative study[13] (n = 24 evaluated subjects), the addition of sertraline (50 mg/d) to clomipramine (150 mg/d) in OCD patients who had not responded to clomipramine monotherapy (150 mg/d) resulted in better tolerability and greater treatment gains relative to an increase in the clomipramine dose to 250 mg/d. In another open-label RCT,[14] the combination of citalopram with clomipramine (n = 9) was associated with greater efficacy than the continuation of citalopram (n = 7) in severely ill patients with OCD, all of whom had previously failed monotherapy trials with clomipramine and fluoxetine. In this RCT, all 9 patients randomly assigned to combination treatment were considered responders.

Marazziti et al[15] treated 20 severely ill, clomipramine-refractory OCD patients using a combination of clomipramine (mean dose = 164 mg/d) and citalopram (mean dose = 38 mg/d). OCD ratings dropped by about 20% after 12 weeks and by > 30% at the end of 48 weeks; about half of the sample was considered to have responded to the combination.

In a 12-week RCT,[16] 54 patients with OCD who had failed fluoxetine monotherapy in the highest recommended or tolerated dose were randomly assigned to receive clomipramine (75 mg/d), quetiapine (200 mg/d), or placebo augmentation of fluoxetine. Clomipramine was dosed at a maximum of 75 mg/d (mean = 56 mg/d), and quetiapine was dosed at a maximum of 200 mg/d. Fluoxetine was dosed at a maximum of 40 mg/d when combined with active medication and at a maximum of 80 mg/d when combined with placebo. OCD ratings decreased by about a quarter with high-dose fluoxetine and with the fluoxetine-clomipramine combination, but there was little improvement in the fluoxetine-quetiapine patients. The response rate in the fluoxetine-clomipramine group was 44%.[16]

Not all studies found combination therapy effective. For example, Diniz et al[17] described a small RCT of 21 evaluable patients with OCD, all of whom had failed to respond adequately to an SSRI. These patients had been randomly assigned to receive SSRI augmentation with either quetiapine (n = 11) or clomipramine (n = 10). Only 1 patient (10%) responded to clomipramine augmentation. In this RCT, most patients received fluoxetine (maximum dose = 40 mg/d) as the SSRI; the target dose of clomipramine was 75 mg/d.

Risks Associated With the SSRI-Clomipramine Combination

SSRI drugs and clomipramine have different adverse effect profiles. What are the adverse effects that have been recorded when clomipramine is combined with an SSRI? Tachycardia (n = 2) and QTc prolongation (n = 2) were described among 7 youths who received an SSRI-clomipramine combination for OCD.[12] Two of 22 patients receiving a combination of fluvoxamine (50–200 mg/d) and clomipramine (50–225 mg/d) experienced myoclonic jerks; these 2 patients were receiving fluvoxamine at the doses of 50–100 mg/d and 100–150 mg/d, and clomipramine at the doses of 100–225 mg/d and 37.5–150 mg/d, respectively. The myoclonic jerks remitted when the medication doses were reduced. The combination was otherwise generally well tolerated, with anticholinergic adverse effects and sedation often reported.[18]

A seizure was reported in a young woman with OCD, 3 months after she attained a fluoxetine dose of 60 mg/d along with a clomipramine dose of 100 mg/d.[19] A seizure occurred in a young man treated with fluoxetine (20 mg/d) for OCD, 4 days after his clomipramine dose was increased from 75 mg/d to 100 mg/d.[20]

In a small RCT,[17] 5 of 15 patients randomly assigned to clomipramine (target dose, 75 mg/d) augmentation of an SSRI (mostly fluoxetine, dosed at 40 mg/d) dropped out early due to severe constipation. Of the remaining 10 who comprised the sample evaluated in the RCT, an elderly male patient receiving fluoxetine (40 mg/d) with clomipramine (50 mg/d) experienced excessive sweating, tremors, and motor agitation, necessitating treatment discontinuation.

In a study[15] of 20 patients, the citalopram-clomipramine combination was associated with a considerable adverse effect burden; problems experienced included anticholinergic symptoms, impairments in sexual functioning, and weight gain. However, these effects were not more than could have been expected given that each drug was used in moderate to

high doses (mean citalopram and clomipramine doses of 38 mg/d and 164 mg/d, respectively). In a recent RCT,[16] 3 of 18 patients receiving a fluoxetine-clomipramine combination developed QTc prolongation and were discontinued from the study.

Mechanisms of Risks Associated With the SSRI-Clomipramine Combination

The SSRI-clomipramine combination may trigger adverse effects through pharmacodynamic and pharmacokinetic mechanisms. The risk of each increases with increasing dose of the drugs in the combination.

When an SSRI and clomipramine are used in low doses, the combination can be expected to be well tolerated. This is because SSRIs are usually associated with a benign adverse effect profile and because low-dose clomipramine is unlikely to cause clinical adverse effects. It is reasonable to assume, however, that adverse effects could be additive; for example, decreased libido or orgasmic dysfunction could be subclinical or mild with the administered dose of each, but could emerge or become more severe when the 2 drugs are combined.[15] The risk of QTc prolongation is another example of a possible additive adverse effect, such as when citalopram[21] and clomipramine[22,23] are combined. It should also be remembered that SSRIs and clomipramine are both serotonergic, and so increasing doses can result in symptoms of serotonergic overstimulation. Examples of such symptoms are anxiety, tremor, akathisia, and insomnia.[24] Such symptoms have been described with the fluoxetine-clomipramine combination.[17]

When the clomipramine dose is moderate to high, the risk of an adverse pharmacokinetic interaction grows. Clomipramine is demethylated by cytochrome P450 (CYP)1A2,[25] CYP3A4,[25] and CYP2C19,[26,27] and clomipramine and its active metabolite desmethylclomipramine are both hydroxylated by CYP2D6.[25,28] Therefore, SSRIs that inhibit multiple enzymes could be expected to raise the levels of and hence the risk of adverse effects with clomipramine. In this context, fluoxetine potently inhibits CYP2D6,[29] moderately to potently inhibits CYP2C19,[29,30] and has a modest to no inhibitory effect on CYP3A4.[31–33] Fluvoxamine potently inhibits CYP1A2,[29] moderately to potently inhibits CYP2C19,[29,30,34,35] modestly inhibits CYP2D6,[29] and mildly inhibits CYP3A4, if at all.[31,36] Paroxetine strongly inhibits CYP2D6,[29] and sertraline inhibits CYP2D6 modestly[37] or not at all.[38]

SSRI inhibitory effects on the CYP enzymes are dose-dependent[29] and more apparent in patients who have mutated *CYP* genes or are extensive metabolizers.[34,35] These SSRIs could therefore pharmacokinetically interact with clomipramine to a clinically significant extent, with greater risk of interaction at higher SSRI dosing levels. Citalopram and escitalopram are weak inhibitors of enzymes such as CYP1A2, CYP2C19, and CYP2D6[37,39] and therefore may not result in clinically significant interactions at usual doses.[40]

Several pharmacokinetic studies illustrate the interactions between SSRIs and clomipramine. For example, in about half of 22 patients treated with a fluvoxamine-clomipramine combination, clomipramine levels were unacceptably high at 500–1,200 ng/mL, although serious side effects were few.[18] Levels were far lower at 11–180 ng/mL with prudent doses of the fluoxetine-clomipramine combination.[16] Fluoxetine can treble the level of a coadministered tricyclic antidepressant (TCA).[41] A review of literature concluded that fluoxetine, fluvoxamine, and paroxetine can markedly raise blood levels of TCA; sertraline also raises TCA levels, but to a lesser extent, and citalopram probably does not affect TCA levels at all.[40]

As far as could be ascertained, only 1 study[18] has evaluated the effect of clomipramine on blood levels of SSRIs. This study addressed fluvoxamine, a drug the levels of which may not rise with clomipramine (see below). Given that clomipramine modestly to potently inhibits CYP2D6[42,43] and given that fluoxetine,[44] sertraline,[45] paroxetine,[46] citalopram,[47,48] and escitalopram,[49] but not fluvoxamine[50] are metabolized by this enzyme (CYP2D6), one might expect that clomipramine would dose-dependently increase the levels and hence the adverse effects of these SSRIs. However, most of the SSRIs are metabolized by multiple enzymes,[51] and so inhibition of CYP2D6 by clomipramine may not have a substantial impact because SSRI metabolism would continue through metabolic pathways mediated by the other CYP enzyme(s). It should also be remembered that SSRIs are generally well tolerated, and so an increase in SSRI levels may not result in clinically significant consequences.

Pharmacodynamic and pharmacokinetic interactions between SSRIs and clomipramine are summarized in Table 1.

Combining SSRIs With Clomipramine: Suggestions for Practice

As would have been obvious from an earlier section, the risks associated with the SSRI-clomipramine combination are not minor; serotonergic overstimulation, QTc prolongation, myoclonic jerks, and seizures are important concerns. This does not mean that the combination is undesirable; rather, their combination needs to be prudent, and close monitoring is advisable.

What does prudence entail? In simplest terms, both drugs need to be prescribed in lower rather than higher doses, because the risks of pharmacodynamic and pharmacokinetic interactions increase as the doses rise. With the exception of citalopram, which increases the risk of QTc prolongation,[21] SSRIs are unlikely to cause serious adverse effects even at higher levels of dosing. However, clomipramine has a narrower therapeutic index, with seizures occurring in 0.48% of patients receiving doses of up to 250 mg/d and 2.1% of patients receiving doses of 300 mg/d and above.[52] Given that fluoxetine coadministration, for example, can treble TCA levels,[41] a 100-mg/d dose of clomipramine may result

Table 1. Pharmacodynamic and Pharmacokinetic Interactions Between SSRIs and Clomipramine

Pharmacodynamic interactions	Many adverse effects are common to clomipramine and certain or all of the SSRIs. These include decrease in libido, orgasmic delay, QTc prolongation, and serotonergic overstimulation. Such adverse effects can therefore be additive in patients who receive an SSRI-clomipramine combination.
Pharmacokinetic interactions	1. Clomipramine is metabolized by CYP1A2, CYP2C19, CYP3A4, and CYP2D6. These enzymes are inhibited by fluoxetine (CYP2D6, CYP2C19; CYP3A4), fluvoxamine (CYP1A2, CYP2C19, CYP2D6, CYP3A4), paroxetine (CYP2D6), and high doses of sertraline (CYP2D6). These SSRIs may raise the levels and hence the risk of adverse effects with clomipramine. Some of these adverse effects, such as seizures, can be life-threatening. Fluoxetine and fluvoxamine may be associated with higher risk of interaction because these drugs inhibit multiple metabolic pathways. Sertraline is unlikely to raise the risk unless dosed at high levels.
	2. Clomipramine inhibits CYP2D6 and may therefore increase the levels and hence the adverse effects of SSRIs that are metabolized by this enzyme. These SSRIs are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. However, the risk of adverse effects (through such an interaction) is low because SSRIs are metabolized through multiple pathways and because SSRIs are generally well tolerated.

Abbreviations: CYP = cytochrome P450, SSRI = selective serotonin reuptake inhibitor.

in blood levels that could be expected with a 300-mg/d dose if this drug is combined with fluoxetine. The implication, therefore, is that when clomipramine is combined with an SSRI that inhibits clomipramine metabolism (Table 1), doses should ideally be limited to a maximum of 75 mg/d, and, at this dose and higher, blood clomipramine level monitoring is desirable.

Browne et al[11] described 2 OCD patients who tolerated and responded to a combination of fluoxetine (60 mg/d) and clomipramine (150–250 mg/d); a third OCD patient tolerated and responded to fluoxetine 20 mg/d and clomipramine 150 mg/d. Amsterdam et al[53] described 11 depressed patients in whom fluoxetine (dose not specified) was augmented with clomipramine. The dose of clomipramine was 300 mg/d in 3 patients, 175–250 mg/d in 3 patients, 100–150 mg/d in 3 patients, and 25–50 mg/d in the remaining 2 patients. Only 1 patient had treatment-limiting adverse effects; these were jitteriness and insomnia, and they occurred at a clomipramine dose of 150 mg/d. These findings, combined with the findings of seizures with the fluoxetine-clomipramine combination at lower doses of clomipramine (100 mg/d)[19,20] and QTc prolongation at even lower doses (75 mg/d),[16] suggest a wide variability in the risk of the interaction across individuals. A reason could be that clomipramine levels at the same dose vary 3- to 14-fold across individuals.[54] It could therefore be a good idea to monitor blood clomipramine levels wherever feasible, and to monitor the electrocardiogram (ECG), as well. Clomipramine doses should not exceed 75 mg/d if blood level monitoring is not possible. Finally, all patients receiving the SSRI-clomipramine combination should be carefully monitored for treatment-emergent adverse effects.

These recommendations apply chiefly to situations in which interactions can be expected (Table 1). What about citalopram? Can this drug be safely administered with clomipramine? Citalopram may not have much effect on clomipramine levels,[40] although some stray reports on pharmacokinetic interactions have been published.[55,56] However, citalopram, especially in higher doses,[21] and clomipramine[22,23] can each increase the QTc interval. The risk of an additive interaction therefore suggests a need for ECG monitoring when these 2 drugs are combined. Clomipramine can probably be safely administered with escitalopram.

Here are a few final practical suggestions. If higher doses of clomipramine are inevitable, divided dosing or the use of sustained-release formulations will result in lower peak blood levels and hence a lower risk of adverse effects that are related to high levels. Lastly, if the risk of seizures is high because the clomipramine dose or level is high (or because the patient has an epileptic diathesis for any other reason), and if the patient needs to be maintained at the current dosing level lest the treatment benefits are lost, it may make sense to add a low to moderate dose of an anticonvulsant drug. This strategy lacks empirical support but could make sense in the refractory OCD patient who is responding to SSRI-clomipramine combination treatment. A precedent is the similar strategy that is adopted in medication-refractory patients with schizophrenia who are receiving high doses of clozapine.[57–60]

Notes on Blood Level Monitoring of Clomipramine

If blood level monitoring is desirable in SSRI-treated patients receiving higher doses of clomipramine, what clomipramine levels are safe and appropriate? Unfortunately, there is little consensus on the subject, and standard reference sources do not provide separate ranges for different indications. One study[61] in 33 patients with OCD found that average plasma levels were 170 ng/mL for clomipramine and 379 ng/mL for desmethylclomipramine at a mean dose of 239 mg/d; levels were higher in responders than nonresponders after 10 weeks of treatment. In contrast, in depression the threshold for satisfactory response was suggested to be about 160–200 ng/mL for clomipramine and desmethylclomipramine combined.[62] Recommendations for clomipramine monitoring could be complicated by the finding that plasma clomipramine levels can vary 3- to 14-fold at a particular dose and schedule of dosing.[54]

Some authorities cite ranges for clomipramine (30–250 ng/mL) and desmethylclomipramine (150–500 ng/mL) separately,[63] whereas others cite levels (150–500 ng/mL) without offering ranges for the drug and its metabolite separately.[64] There is also no consensus on whether blood

should be drawn 12 hours after the last dose[18,63] or at trough level. However, Stein and Fineberg[65] suggest that trough levels of clomipramine and desmethylclomipramine combined should usually be kept below 450 ng/mL to minimize toxicity.

REFERENCES

1. Geller DA, Biederman J, Stewart SE, et al. Which SSRI? a meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. *Am J Psychiatry*. 2003;160(11):1919–1928.
2. Feinberg M. Clomipramine for obsessive-compulsive disorder. *Am Fam Physician*. 1991;43(5):1735–1738.
3. Bandelow B, Sher L, Bunevicius R, et al; WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. *Int J Psychiatry Clin Pract*. 2012;16(2):77–84.
4. Bloch MH, McGuire J, Landeros-Weisenberger A, et al. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Mol Psychiatry*. 2010;15(8):850–855.
5. Marazziti D, Consoli G. Treatment strategies for obsessive-compulsive disorder. *Expert Opin Pharmacother*. 2010;11(3):331–343.
6. Walsh KH, McDougle CJ. Pharmacological augmentation strategies for treatment-resistant obsessive-compulsive disorder. *Expert Opin Pharmacother*. 2004;5(10):2059–2067.
7. Abudy A, Juven-Wetzler A, Zohar J. Pharmacological management of treatment-resistant obsessive-compulsive disorder. *CNS Drugs*. 2011;25(7):585–596.
8. Dold M, Aigner M, Lanzenberger R, et al. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2013;16(3):557–574.
9. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
10. Simeon JG, Thatte S, Wiggins D. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. *Psychopharmacol Bull*. 1990;26(3):285–290.
11. Browne M, Horn E, Jones TT. The benefits of clomipramine-fluoxetine combination in obsessive compulsive disorder. *Can J Psychiatry*. 1993;38(4):242–243.
12. Figueroa Y, Rosenberg DR, Birmaher B, et al. Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive-compulsive disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 1998;8(1):61–67.
13. Ravizza L, Barzega G, Bellino S, et al. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). *Psychopharmacol Bull*. 1996;32(4):677–682.
14. Pallanti S, Quercioli L, Paiva RS, et al. Citalopram for treatment-resistant obsessive-compulsive disorder. *Eur Psychiatry*. 1999;14(2):101–106.
15. Marazziti D, Golia F, Consoli G, et al. Effectiveness of long-term augmentation with citalopram to clomipramine in treatment-resistant OCD patients. *CNS Spectr*. 2008;13(11):971–976.
16. Diniz JB, Shavitt RG, Fossaluza V, et al. A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2011;31(6):763–768.
17. Diniz JB, Shavitt RG, Pereira CA, et al. Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial. *J Psychopharmacol*. 2010;24(3):297–307.
18. Szegedi A, Wetzel H, Leal M, et al. Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. *J Clin Psychiatry*. 1996;57(6):257–264.
19. Sternbach H. Fluoxetine-clomipramine interaction. *J Clin Psychiatry*. 1995;56(4):171–172.
20. Andrade C. Fluoxetine, risperidone and seizures. *Indian J Psychol Med*. 1999;22(1):61–63.
21. Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288.
22. Leonard HL, Meyer MC, Swedo SE, et al. Electrocardiographic changes during desipramine and clomipramine treatment in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34(11):1460–1468.
23. Okayasu H, Ozeki Y, Fujii K, et al. Pharmacotherapeutic determinants for QTc interval prolongation in Japanese patients with mood disorder. *Pharmacopsychiatry*. 2012;45(7):279–283.
24. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112–1120.
25. Nielsen KK, Flinois JP, Beaune P, et al. The biotransformation of clomipramine in vitro, identification of the cytochrome P450s responsible for the separate metabolic pathways. *J Pharmacol Exp Ther*. 1996;277(3):1659–1664.
26. Yokono A, Morita S, Someya T, et al. The effect of CYP2C19 and CYP2D6 genotypes on the metabolism of clomipramine in Japanese psychiatric patients. *J Clin Psychopharmacol*. 2001;21(6):549–555.
27. de Vos A, van der Weide J, Loovers HM. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. *Pharmacogenomics J*. 2011;11(5):359–367.
28. Balant-Gorgia AE, Balant LP, Genet C, et al. Importance of oxidative polymorphism and levomepromazine treatment on the steady-state blood concentrations of clomipramine and its major metabolites. *Eur J Clin Pharmacol*. 1986;31(4):449–455.
29. Jeppesen U, Gram LF, Vistisen K, et al. Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol*. 1996;51(1):73–78.
30. Harvey AT, Preskorn SH. Fluoxetine pharmacokinetics and effect on CYP2C19 in young and elderly volunteers. *J Clin Psychopharmacol*. 2001;21(2):161–166.
31. Lam YW, Alfaro CL, Ereshefsky L, et al. Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. *J Clin Pharmacol*. 2003;43(11):1274–1282.
32. DeVane CL, Donovan JL, Liston HL, et al. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol*. 2004;24(1):4–10.
33. Lutz JD, Vandenbrink BM, Babu NK, et al. Stereoselective inhibition of CYP2C19 and CYP3A4 by fluoxetine and its metabolite: implications for risk assessment of multiple time-dependent inhibitor systems [published online ahead of print June 19, 2013]. *Drug Metab Dispos*. 2013.
34. Suzuki Y, Shioiri T, Muratake T, et al. Effects of concomitant fluvoxamine on the metabolism of alprazolam in Japanese psychiatric patients: interaction with CYP2C19 mutated alleles. *Eur J Clin Pharmacol*. 2003;58(12):829–833.
35. Yasui-Furukori N, Takahata T, Nakagami T, et al. Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol*. 2004;57(4):487–494.
36. Olesen OV, Linnet K. Fluvoxamine-Clozapine drug interaction: inhibition in vitro of five cytochrome P450 isoforms involved in clozapine metabolism. *J Clin Psychopharmacol*. 2000;20(1):35–42.
37. Preskorn SH, Greenblatt DJ, Flockhart D, et al. Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. *J Clin Psychopharmacol*. 2007;27(1):28–34.
38. Alfaro CL, Lam YW, Simpson J, et al. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. *J Clin Pharmacol*. 2000;40(1):58–66.
39. von Moltke LL, Greenblatt DJ, Grassi JM, et al. Citalopram and desmethylcitalopram in vitro: human cytochromes mediating transformation, and cytochrome inhibitory effects. *Biol Psychiatry*. 1999;46(6):839–849.
40. Taylor D. Selective serotonin reuptake inhibitors and tricyclic antidepressants in combination: interactions and therapeutic uses. *Br J Psychiatry*. 1995;167(5):575–580.
41. Nelson JC. Combined treatment strategies in psychiatry. *J Clin Psychiatry*. 1993;54(suppl):42–49, discussion 55–56.
42. Lamard L, Pérault MC, Bouquet S, et al. Cytochrome p450 IID6, its role in psychopharmacology. *Ann Med Psychol (Paris)*. 1995;153(2):140–143.
43. Vandel P, Haffen E, Nezelof S, et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. *Hum Psychopharmacol*. 2004;19(5):293–298.
44. Margolis JM, O'Donnell JP, Mankowski DC, et al. *R*-, *S*-, and racemic fluoxetine N-demethylation by human cytochrome P450 enzymes. *Drug Metab Dispos*. 2000;28(10):1187–1191.
45. Obach RS, Cox LM, Tremaine LM. Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. *Drug Metab Dispos*. 2005;33(2):262–270.
46. Foster RH, Goa KL. Paroxetine: a review of its pharmacology and therapeutic

potential in the management of panic disorder. *CNS Drugs*. 1997;8(2):163–188.
47. Rochat B, Amey M, Gillet M, et al. Identification of three cytochrome P450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. *Pharmacogenetics*. 1997;7(1):1–10.
48. Olesen OV, Linnet K. Studies on the stereoselective metabolism of citalopram by human liver microsomes and cDNA-expressed cytochrome P450 enzymes. *Pharmacology*. 1999;59(6):298–309.
49. Caccia S. Metabolism of the newest antidepressants: comparisons with related predecessors. *IDrugs*. 2004;7(2):143–150.
50. van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet*. 1995;29(suppl 1):1–9.
51. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41(2):89–295.
52. McTavish D, Benfield P. Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs*. 1990;39(1):136–153.
53. Amsterdam JD, García-España F, Rosenzweig M. Clomipramine augmentation in treatment-resistant depression. *Depress Anxiety*. 1997;5(2):84–90.
54. Jones RB, Luscombe DK. Plasma level studies with clomipramine (Anafranil). *J Int Med Res*. 1977;5(suppl):98–107.
55. Haffen E, Vandel P, Broly F, et al. Citalopram: an interaction study with clomipramine in a patient heterozygous for CYP2D6 genotype. *Pharmacopsychiatry*. 1999;32(6):232–234.
56. Haffen E, Vandel P, Bonin B, et al. Citalopram pharmacokinetic interaction with clomipramine. UDP-glucuronosyltransferase inhibition? a case report. *Therapie*. 1999;54(6):768–770.
57. Toth P, Frankenburg FR. Clozapine and seizures: a review. *Can J Psychiatry*. 1994;39(4):236–238.
58. Balen RM, Procyshyn RM. Valproic acid for seizure prophylaxis during clozapine therapy: where's the evidence? *Int J Psychiatry Clin Pract*. 1999;3(4):249–251.
59. Usiskin SI, Nicolson R, Lenane M, et al. Gabapentin prophylaxis of clozapine-induced seizures. *Am J Psychiatry*. 2000;157(3):482–483.
60. Sparshatt A, Whiskey E, Taylor D. Valproate as prophylaxis for clozapine-induced seizures: survey of practice. *Psychiatrist*. 2008;32:262–265.
61. Mavissakalian M, Jones B, Olson S, et al. The relationship of plasma clomipramine and N-desmethylclomipramine to response in obsessive-compulsive disorder. *Psychopharmacol Bull*. 1990;26(1):119–122.
62. Faravelli C, Ballerini A, Ambonetti A, et al. Plasma levels and clinical response during treatment with clomipramine. *J Affect Disord*. 1984;6(1):95–107.
63. Bhagwagar Z, Heninger GR. Antidepressants. In: Gelder MG, Andreasen NC, Lopez-Ibor JJ, et al, eds. *New Oxford Textbook of Psychiatry*. 2nd ed. Oxford, UK: Oxford University Press; 2009:1185–1198.
64. Baldessarini RJ. Drugs and the treatment of psychiatric disorders: depression and anxiety disorders. In: Hardman JG, Limbrd LE, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:447–483.
65. Stein DJ, Fineberg NA. *Obsessive-Compulsive Disorder*. Oxford, UK: Oxford University Press; 2007.