Serotonin-Selective Reuptake Inhibitors and Nonsteroidal Anti-Inflammatory Drugs—Important Considerations of Adverse Interactions Especially for the Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Theoharis C. Theoharides, MS, MD, PhD, FAAAAI,†‡§*
Shahrzad Asadi, PharmD, Zuyi Weng, BS, DipGradSci,*||*
*and Bodi Zhang, MD, MPH, PhD**

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) affects as many as 1 in 100 women in the United States, but its pathogenesis remains largely unknown.[1–5] ME/CFS is associated with depression, inability to concentrate (brain fog), and pain,[6] necessitating the concurrent use of antidepressants, especially serotonin-selective reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs).[7,8] Considerable evidence, however, suggests that the older tricyclic antidepressants (TCAs) may be more efficacious than SSRIs in ME/CFS[9–11] and in fibromyalgia.[12,13] Moreover, TCAs are also effective in managing chronic pain.[14] Evidence presented in this issue further indicates that TCAs can also inhibit activation of mast cells.[15] These unique immune cells that are found in all tissues, but also especially in the diencephalon, were hypothesized to be involved in ME/CFS.[16]

It has been well known that SSRIs, but not the TCAs, increase the risk of gastrointestinal bleeding when given alone[17,18] and further increase this risk when administered together with NSAIDs (Fig. 1).[17–24] However, the underlying mechanism is still unknown. Interestingly, TCAs do not seem to do so maybe because of their antagonism of histamine-1 receptors that are known to be protective against gastritis. In a recent article, coadministration of the NSAIDs ibuprofen or acetylsalicyclic acid with SSRIs blocked the behavioral response to SSRIs, but not to the TCA desipramine, in a rodent model

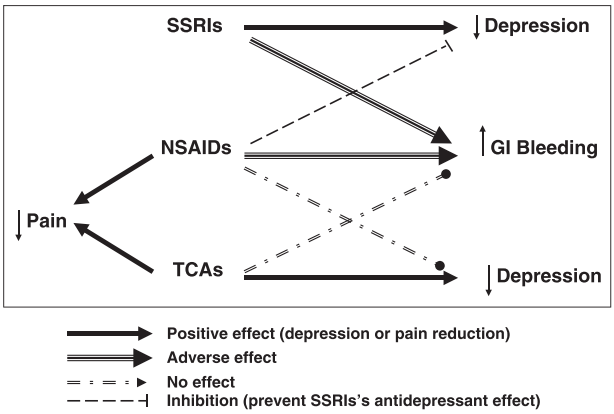

FIGURE 1. Diagrammatic representation of suggested interactions among SSRIs, TCAs, and NSAIDs.

From the *Molecular Immunopharmacology and Drug Discovery Laboratory, Departments of Molecular Physiology and Pharmacology, †Internal Medicine, ‡Psychiatry, §Biochemistry, and ||Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine and Tufts Medical Center, Boston, MA.
Reprints: Theoharis C. Theoharides, MS, MD, PhD, FAAAAI, Department of Molecular Physiology and Pharmacology, Room M&V 208, Tufts University School of Medicine, 136 Harrison Ave, Boston, MA 02111 (e-mail: theoharis.theoharides@tufts.edu).

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e318225848c

of depression.[25] SSRIs were further shown to exert their antidepressant effect through an increased level of p11, a regulator protein known to interact with serotonin receptors. SSRI–related p11 increases were apparently dependent on signaling by the cytokines interferon-γ and tumor necrosis factor (TNF); NSAIDs inhibited the SSRI-induced step-activating cytokines, decreasing the antidepressant response, but did not affect the antidepressant action of TCAs.[25] The authors mention in their discussion that similar findings were noted in a clinical population studied retrospectively. Although the decrease in clinical effectiveness was evident, the mechanism of these interactions is not yet clear, especially because depression has increasingly been associated with an inflammatory state and increased TNF levels.[26–28] One would, therefore, have expected antidepressants to reduce rather than increase TNF revels. In fact, there is some suggestive evidence that cyclooxygenase 2 inhibitors may have antidepressant actions themselves.[29]

The authors further state that TNF may increase brain-derived neurotrophic factor (BDNF) that contributes to the antidepressant action. However, the flavonoid luteolin (5,7,3′,4′-tetrahydroxyflavone) prevents human mast cell release of pro-inflammatory molecules,[30] including TNF (Fig. 2), and human mast cell–dependent T-cell activation mediated through TNF.[31] Yet, a close structural analogue of luteolin (7, 8-dihydroxyflavone) can mimic the action of BDNF.[32] Luteolin inhibits microglia with concomitant spatial working memory increases in mice[33] and also protects dopaminergic neurons.[34] These findings are apparently contrary to the hypothesis presented by the authors. One possible explanation may be that luteolin may increase BDNF independently of any action on TNF levels.

Instead of NSAIDs, one may consider the use of certain natural flavonoid compounds[35] that not only do not share any properties with NSAIDs but also have been reported by some to have beneficial actions in animal models of ME/CFS.[36,37] For instance, epigallocatechin and curcumin were reported to prevent the development of symptoms in a rodent model of ME/CFS.[38,39] A dietary formulation containing mostly luteolin was presented at a recent National Institutes of Health (NIH)–sponsored ME/CSF conference (http://www.prohealth.com/library/showarticle.cfm?libid=16032) and is already being used by patients.

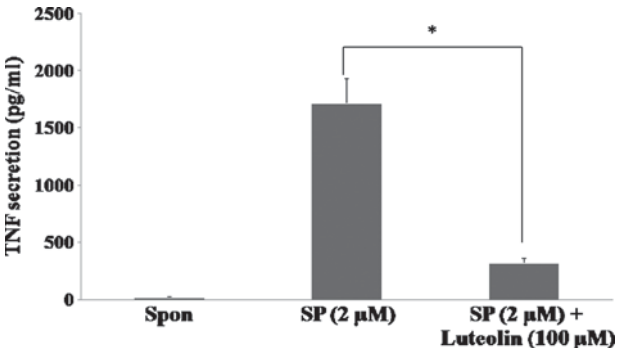

FIGURE 2. Effect of luteolin on substance P–induced TNF secretion from cultured human LAD2 mast cells, kindly supplied by Dr A. Kirshembaum (NIH, Bethesda, MD) and grown in StemPro medium (Invitrogen, Carlsbad, CA) and supplemented with stem cell factor, kindly supplied by Biovitrum AB (Stockholm, Sweden). Luteolin dissolved in dimethyl sulfoxide was used at a final concentration of 100 μM for 30 minutes before SP (2 μM), and TNF was measured in the supernatant fluid 24 hours later by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). Viability was higher than 95% (n = 3, $*P < 0.05$ using Mann-Whitney *U* test). Spon indicates spontaneous release from control, unstimulated cells.

Health providers should be aware of these potential adverse interactions and may prefer to elect non-SSRIs when there is need to administer both antidepressants and analgesics, or choose non-NSAID analgesics, such as tramadol and/or anti-inflammatory flavonoids, as the case is for ME/CFS.

AUTHOR DISCLOSURE INFORMATION

Results presented in Figure 2 were obtained through support by NIH grant 5R01NS71361 to Dr Theoharides. Dr Zhang is supported in part by a fellowship from Galenica SA (Athens, Greece). The authors declare that they have no competing interests. Dr Theoharides is the inventor of patent applications US 11/214,831 covering the diagnosis and treatment of diseases associated with brain inflammation and of the luteolin dietary supplement formulation NeuroProtek (US Trademark 3,225,924), assigned to Theta Biomedical Consulting and Development Co, Inc (Brookline, Mass).

REFERENCES

1. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med*. 1994;121:953–959.
2. Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry*. 2003;160:221–236.
3. Jason LA, Corradi K, Torres-Harding S, et al. Chronic fatigue syndrome: the need for subtypes. *Neuropsychol Rev*. 2005;15:29–58.
4. Santhouse AM, Hotopf M, David AS. Chronic fatigue syndrome. *BMJ*. 2010;340:c738.
5. Avellaneda FA, Perez MA, Izquierdo MM, et al. Chronic fatigue syndrome: aetiology, diagnosis and treatment. *BMC Psychiatry*. 2009;9(Suppl 1):S1.
6. Van HB, Kempke S, Luyten P. Psychiatric aspects of chronic fatigue syndrome and fibromyalgia. *Curr Psychiatry Rep*. 2010;12:208–214.
7. Rimes KA, Chalder T. Treatments for chronic fatigue syndrome. *Occup Med (Lond)*. 2005;55:32–39.
8. Pae CU, Marks DM, Patkar AA, et al. Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants. *Expert Opin Pharmacother*. 2009;10:1561–1570.
9. Mease PJ. Further strategies for treating fibromyalgia: the role of serotonin and norepinephrine reuptake inhibitors. *Am J Med*. 2009;122:S44–S55.
10. Staud R. Pharmacological treatment of fibromyalgia syndrome: new developments. *Drugs*. 2010;70:1–14.
11. Pae CU, Marks DM, Patkar AA, et al. Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants. *Expert Opin Pharmacother*. 2009;10:1561–1570.
12. Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA*. 2009;301:198–209.
13. Hameroff SR, Cork RC, Weiss JL, et al. Doxepin effects on chronic pain and depression: a controlled study. *Clin J Pain*. 1985;1:171–176.
14. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. *J Clin Pharmacol*. 2011. [Epub ahead of print].
15. Clemons A, Vasiadi M, Kempuraj D, et al. Amitriptyline and prochlorperazine inhibit proinflammatory mediator release from human mast cells: possible relevance to chronic fatigue syndrome. *J Clin Psychopharmacol*. 2011;31:385–387.
16. Theoharides TC, Papaliodis D, Tagen M, et al. Chronic fatigue syndrome, mast cells, and tricyclic antidepressants. *J Clin Psychopharmacol*. 2005;25:515–520.

17. Andrade C, Sandarsh S, Chethan KB, et al. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry.* 2010;71:1565–1575.
18. Targownik LE, Bolton JM, Metge CJ, et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol*. 2009;104:1475–1482.
19. Bell JS, Taipale HT, Soini H, et al. Concomitant use of SSRIs, NSAIDs/aspirin and gastroprotective drugs among residents of long-term care facilities: a medical record reviewfs. *Clin Drug Investig*. 2011;31:337–344.
20. de Jong JC, van den Berg PB, Tobi H, et al. Combined use of SSRIs and NSAIDs increases the risk of gastrointestinal adverse effects. *Br J Clin Pharmacol*. 2003;55:591–595.
21. Weinrieb RM, Auriacombe M, Lynch KG, et al. Selective serotonin re-uptake inhibitors and the risk of bleeding. *Expert Opin Drug Saf.* 2005;4:337–344.
22. Mort JR, Aparasu RR, Baer RK. Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammatory drugs: review of the literature. *Pharmacotherapy.* 2006;26:1307–1313.
23. Helin-Salmivaara A, Huttunen T, Gronroos JM, et al. Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population. *Eur J Clin Pharmacol*. 2007;63:403–408.
24. Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*. 2008;27:31–40.
25. Warner-Schmidt JL, Vanover KE, Chen EY, et al. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. *Proc Natl Acad Sci U S A*. 2011;108(22):9262–9267.
26. Theoharides TC, Weinkauf C, Conti P. Brain cytokines and neuropsychiatric disorders. *J Clin Psychopharmacol*. 2004;24:577–581.
27. Dinan TG. Inflammatory markers in depression. *Curr Opin Psychiatry.* 2009;22:32–36.
28. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009;65:732–741.
29. Muller N. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Investig Drugs*. 2010;11:31–42.
30. Kempuraj D, Madhappan B, Christodoulou S, et al. Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. *Br J Pharmacol*. 2005;145:934–944.
31. Kempuraj D, Tagen M, Iliopoulou BP, et al. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells. *Br J Pharmacol*. 2008;155:1076–1080.
32. Jang SW, Liu X, Yepes M, et al. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci U S A*. 2010;107:2687–2692.
33. Jang S, Dilger RN, Johnson RW. Luteolin inhibits microglia and alters hippocampal-dependent spatial working memory in aged mice. *J Nutr.* 2010;140:1892–1898.
34. Chen HQ, Jin ZY, Wang XJ, et al. Luteolin protects dopaminergic neurons from inflammation-induced injury through inhibition of microglial activation. *Neurosci Lett*. 2008;448:175–179.
35. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol Rev.* 2000;52:673–751.
36. Kuo YH, Tsai WJ, Loke SH, et al. Astragalus membranaceus flavonoids (AMF) ameliorate chronic fatigue syndrome induced by food intake restriction plus forced swimming. *J Ethnopharmacol*. 2009;122:28–34.
37. Singh A, Naidu PS, Gupta S, et al. Effect of natural and synthetic antioxidants in a mouse model of chronic fatigue syndrome. *J Med Food*. 2002;5:211–220.
38. Sachdeva AK, Kuhad A, Tiwari V, et al. Epigallocatechin gallate ameliorates chronic fatigue syndrome in mice: behavioral and biochemical evidence. *Behav Brain Res*. 2009;205:414–420.
39. Gupta A, Vij G, Sharma S, et al. Curcumin, a polyphenolic antioxidant, attenuates chronic fatigue syndrome in murine water immersion stress model. *Immunobiology.* 2009;214:33–39.