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

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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/CFS9–11 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 alone17,18 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 acetylsalicylic 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.
of depression.\textsuperscript{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-\(\gamma\) 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.\textsuperscript{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.\textsuperscript{26–28} One would, therefore, have expected antidepressants to reduce rather than increase TNF levels. In fact, there is some suggestive evidence that cyclooxygenase 2 inhibitors may have antidepressant actions themselves.\textsuperscript{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,\textsuperscript{30} including TNF (Fig. 2), and human mast cell–dependent T-cell activation mediated through TNF.\textsuperscript{31} Yet, a close structural analogue of luteolin (7,8-dihydroxyflavone) can mimic the action of BDNF.\textsuperscript{32} Luteolin inhibits microglia with concomitant spatial working memory increases in mice\textsuperscript{33} and also protects dopaminergic neurons.\textsuperscript{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\textsuperscript{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.\textsuperscript{36,37} For instance, epigallocatechin and curcumin were reported to prevent the development of symptoms in a rodent model of ME/CFS.\textsuperscript{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.

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 analogues, such as tramadol and/or anti-inflammatory flavonoids, as the case is for ME/CFS.

**AUTHOR DISCLOSURE INFORMATION**

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**REFERENCES**


