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LETTER TO THE EDITOR

Neonatal signs following exposure to SSRIs

Dear Editor

Moses-Kolko *et al*. (2005) reported that late (final trimester of pregnancy) exposure of serotonin reuptake inhibitor (SRI) carries an overall risk ratio of 3.0 for a neonatal behavioral syndrome as compared with early gestational SRI exposure or no exposure. Eleven (61%) of the 18 cases of SRI-related neonatal signs were associated with paroxetine exposure. Furthermore, neonatal behavioral signs across the cohort studies and the case series were similar to those reported in the single case reports (Moses-Kolko *et al*., 2005). Furthermore, Sanz *et al*. (2005) reported recently the association between neonatal withdrawal syndrome and maternal use of SRIs, especially paroxetine. They identified a total of 102 cases of SRI use associated with either neonatal convulsions or withdrawal syndrome. Paroxetine was the most commonly reported SRI with these adverse side effects. Cases were also reported for fluoxetine, sertraline, and citalopram, but not for any of the other SRIs including fluvoxamine (Sanz *et al*., 2005). They conclude that paroxetine should not be used in pregnancy or, if used, should be given at the lowest effective dose (Sanz *et al*., 2005). These two authors suggested that a moderate affinity of paroxetine at muscarinic acetylcholine receptors could contribute to neonatal behavioral syndromes and withdrawal syndrome associated with paroxetine use (Moses-Kolko *et al*., 2005; Sanz *et al*., 2005).

Sigma-1 receptors are brain-enriched endoplasmic reticulum proteins that are implicated in certain psychiatric disorders including depression and anxiety (Hayashi and Su, 2004; Hashimoto and Ishiwata, 2005). Sigma-1 receptors modulate a number of neurotransmitter systems, including noradrenergic, glutamatergic, and cholinergic systems (Hayashi and Su, 2004; Hashimoto and Ishiwata, 2005). We reported that SRIs possessed high to moderate affinities at sigma-1 receptors in the brain (Narita *et al*., 1996). The rank order of potency of drugs for sigma-1 receptors was as follows: fluvoxamine (Ki = 36 nmol/L) > sertraline > fluoxetine > citalopram > paroxetine (Ki = l893 nmol/L). Sigma-1 receptor agonists can improve acetylcholine (e.g., anti-muscarinic drugs)-related deficits such as memory and cognition in rodent models, and are also effective in animal models of depression (Hayashi and Su, 2004; Hashimoto and Ishiwata, 2005). Additionally, fluvoxamine acts as an agonist at sigma-1 receptors although it is unknown whether other SRIs are agonists at sigma-1 receptors (Hayashi and Su, 2004; Hashimoto and Ishiwata, 2005). Taken together, it seems that agonistic activity of fluvoxamine at sigma-1 receptors might, in part, play a role in the lack of these side effects of fluvoxamine although further studies using selective sigma-1 receptor agonists would be necessary. Therefore, it is likely that SRIs (e.g., fluvoxamine) with high affinity at sigma-1 receptors might be useful for the treatment of perinatally depressed women.

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