Paroxetine: Into Oblivion?

To the Editor: Paroxetine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the US Food and Drug Administration (FDA) for adult depression, obsessive-compulsive disorder, anxiety disorders, and vasomotor changes of menopause. Nonetheless, its clinical use has recently fallen into disfavor.[1] Moreover, the FDA advised against its use in the child and adolescent population.

This aversive attitude in practice might be ascribed to a multitude of reasons related to its pharmacologic properties. These properties might be broadly subdivided into anticholinergic actions, cytochrome P450 2D6 (CYP2D6) inhibitory properties, and a miscellaneous group.

Anticholinergic actions. Paroxetine is the most anticholinergic of the SSRIs on the market, which is especially problematic in the geriatric population due to its anticognitive properties. Paroxetine has been associated with highest weight gain among the SSRIs,[2] mainly during the first 12 months of treatment. Antimuscarinic and sedative properties of paroxetine might be contributory to weight gain. Also, paroxetine is infamous for sexual dysfunction (up to 75% of patients), and it is more likely to cause disorders of arousal and anorgasmia than other SSRIs.

CYP2D6 inhibitory properties. Paroxetine is a potent CYP2D6 inhibitor, so pharmacokinetic interactions with drugs that are substrate to CYP2D6 are commonplace (eg, risperidone). This pharmacological portfolio, especially in poor metabolizers, may translate into clinical toxicity. Furthermore, inhibiting CYP2D6 may render drugs like tamoxifen in breast cancer ineffective by blocking its conversion into endoxifen.

Paroxetine is notorious for its discontinuation syndrome, which may, in part, be due to its ability to inhibit its own metabolism[3]—as it is a substrate for CYP2D6—hence, the rapid decline of levels and discontinuation symptoms once it is rapidly stopped.

Miscellaneous. Paroxetine has been tied to activation of suicidal ideations most often in youth. The FDA downgraded paroxetine to pregnancy category D, as association with ventricular septal defects has been reported. Notably, in the child and adolescent population, 2 randomized controlled trials[4,5] of paroxetine for juvenile depression were negative. Last, but not least, paroxetine has been demonstrated to decrease the heart rate variability, which has been linked to increased cardiovascular mortality.[6]

Conclusion. In all, I surmise that the problems and inherent risks associated with paroxetine use speak to the idea of a psychotropic "falling off the track" and render it a less appealing choice in clinical practice compared to far more efficacious and safer alternatives already available on market. It is then incumbent on clinicians to be vigilant and prudent when prescribing paroxetine, especially in child and adolescent, female, and geriatric populations.

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