**Adverse Effects**

SSRI antidepressants: extrapyramidal reactions.

- **Dose increase.**

A review published in 2015 identified 91 reports of extrapyramidal reactions attributed to serotonin reuptake inhibitor antidepressants published between 1998 and May 2015 (1).

The extrapyramidal reactions reported were akathisia (17 patients), dyskinesia (18 patients) including tardive dyskinesia, dystonia (27 patients), parkinsonism (19 patients), and a combination of several types of extrapyramidal reaction (10 patients). In half of the cases, the disorder occurred within 7 days after initiating the treatment or increasing the dose (1).

In most cases, the drug implicated was a “selective” serotonin reuptake inhibitor (SSRI): citalopram or its enantiomer escitalopram (22% of cases), fluoxetine (21%) or sertraline (15%). Serotonin and noradrenaline reuptake inhibitors were also implicated: venlafaxine (12%) or duloxetine (5%). In 14% of cases the patient was taking no other medication (1).

Extrapyramidal disorders are known adverse effects of antidepressants with serotonergic effects. In the 1950s, cases of “muscle hypertonia” and “hypermotility” were described with monoamine oxidase inhibitors (MAOIs) (2). Cases of extrapyramidal reactions were later linked to imipramine (2).

If tremor, dystonia or abnormal movements develop in a patient taking a serotonergic antidepressant, the role of the drug must be suspected and its discontinuation suggested, at least temporarily, to test this hypothesis, while bearing in mind the risk of a withdrawal syndrome.

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Gliptins: disabling joint pain

- **Poor harm-benefit balance.**

In August 2015, the US Food and Drug Administration (FDA) issued a safety warning about 33 reports of severe joint pain linked to gliptins, a group of glucose-lowering drugs (1). The pain started within the first month of treatment in 22 cases. 10 patients were hospitalised for disabling pain. In 23 cases, the pain regressed within a month after gliptin cessation. Joint pain recurred in all 8 cases of gliptin rechallenge, including 6 cases in which a different gliptin was used (1).

Manifestations suggestive of inflammation or an immune reaction were observed in some patients: fever, rash, oedema, elevated erythrocyte sedimentation rate (1 case) or elevated C-reactive protein (CRP) (1 case). Some findings suggested an autoimmune reaction: anti-nuclear antibodies (2 cases), and anti-neutrophil cytoplasmic antibodies (1 case). Certain patients received corticosteroids, methotrexate or another immunosuppressant to treat their joint pain.

Gliptins inhibit dipeptidyl peptidase (DPP-4) and thereby prolong the action of gut hormones (incretins) that stimulate insulin secretion (2). DPP-4 is similar to CD26, a protein on the surface of lymphocytes that modulates their function. The action of gliptins on CD26 is probably implicated in their immunological effects (2). On the one hand they provoke hypersensitivity reactions, and on the other hand they have immunosuppressant effects and increase the risk of infection, in particular urinary and upper respiratory tract infections. These apparently inflammatory gliptin-associated joint disorders may share a similar mechanism.

Gliptins have a long list of adverse effects and any long-term clinical benefits have yet to be proven (2). Gliptins have an unfavourable harm-benefit balance.

If a glitin-treated patient develops joint pain, recognising the drug’s role and stopping this treatment can relieve the pain and avoid exposure to antimuscarinic or anti-inflammatory drugs and to their adverse effects.

Selected references from Prescrire’s literature search.