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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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Selected references from Prescrire's literature search.

1- Hawthorne JM and Caley CF "Extrapyramidal reactions associated with serotonergic antidepressants" *Ann Pharmacother* 2015; **49** (10): 1136-1152.

2- Prescrire Rédaction "Effets extrapyramidaux des antidépresseurs inhibiteurs de la recapture de la sérotonine" *Rev Prescrire* 2001; **21** (215): 201-203.

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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 dipeptidase (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 gliptin-treated patient develops joint pain, recognising the drug's role and stopping this treatment can relieve the pain and avoid exposure to antirheumatic or anti-inflammatory drugs and to their adverse effects.

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Selected references from Prescrire's literature search.

1- U.S. Food and Drug Administration "FDA drug safety communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain" 8 August 2015. www.fda.gov accessed 25 September 2015: 4 pages.

2- Prescrire Rédaction "4-1-9. Patients sous sitagliptine, vildagliptine, saxagliptine ou linagliptine" *Rev Prescrire* 2014; **34** (374 suppl. interactions médicamenteuses).

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Mirabegron: hypertension, stroke

● A poor option in urinary incontinence.



Mirabegron is a beta-3 adrenoceptor agonist approved for the symptomatic relief of certain types of urinary incontinence. Cardiovascular adverse effects are expected, given its mechanism of action and the fact that, in clinical use, receptor selectivity is only relative (1).

Initial evaluation data showed that *mirabegron* can provoke arrhythmia, QT prolongation and hypertension (1).

Since its market introduction, *mirabegron* has been implicated in cases of severe hypertension and hypertensive crisis associated with cardiovascular disorders, including stroke (2).

In October 2015, the European public pharmacovigilance database (www.adrreports.eu) contained 130 reports of hypertension linked to *mirabegron* submitted by health professionals and 43 submitted by patients, and 14 cases of hypertensive crisis (3).

The efficacy of *mirabegron* in urinary incontinence is minimal, and similar to that of antimuscarinic drugs. Drugs are of little value in this situation. *Mirabegron*'s minor efficacy will not usually justify exposing patients to the risk of hypertensive crisis, even for severe urinary incontinence. A better choice in these cases is a better established antimuscarinic drug.

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Selected references from Prescrire's literature search.

1- Prescrire Editorial Staff "Mirabegron. Poorly effective in urge urinary incontinence" *Prescrire Int* 2016; **25** (167): 8-9.

2- MHRA "Mirabegron (Betmiga): risk of severe hypertension and associated cerebrovascular and cardiac events" *Drug Safety Update* 2015; **9** (3): 1.

3- EMA "Suspected adverse drug reaction reports for substances. Mirabegron" October 2015. www.adrreports.eu accessed 23 November 2015.