THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Clinical Pearls from Prescrire

The *Therapeutics Letter* is only one of many independent bulletins in different countries that provide evidence-based information to physicians, pharmacists and the public about drug treatments. In issue #60 of the *Therapeutics Letter* (Oct-Dec 2006) we published the first *Clinical Pearls from Prescrire*[1], a Letter that highlighted messages from the English *Prescrire International*, which is a translation of the French independent drug bulletin, *La Revue Prescrire*. Once again, in this *Therapeutics Letter* we present selected direct quotes published in recent issues of *Prescrire International*. If you find this information useful, we encourage you to subscribe to *Prescrire International*: http://english.prescrire.org/en/83/178/0/0/About.aspx

Arterial hypertension: don't expose patients to the adverse effects of aliskiren (Rasilez*) [2]

In the absence of proven efficacy based on robust clinical criteria, and given the risk of severe adverse effects, the use of aliskiren to treat arterial hypertension cannot be justified.

NOT ACCEPTABLE

The marketing authorization for aliskiren, an antihypertensive drug, relies on surrogate endpoints, i.e. blood pressure levels, and not on robust clinical outcomes, such as the reduction of cardiovascular events. Its adverse effects profile is no more favourable than that of other antihypertensive drugs with similar action mechanisms (angiotensin-converting enzyme inhibitors (also called ACE inhibitors) and angiotensin II receptor blockers).

This profile has become all the more worrying since the interruption, at the end of December 2011, of a clinical trial comparing aliskiren with placebo, following an excessive number of sometimes fatal adverse events, such as cardiovascular disorders and renal failure. Furthermore, this trial did not demonstrate aliskiren's superiority over placebo.

In practice, given aliskiren's uncertain harm-benefit balance, it is better not to prescribe it for hypertension, either alone or in combination, but rather to rely on antihypertensives whose efficacy in reducing cardiovascular events has been proven.

Drugs for Alzheimer's disease: best avoided (Reassessment) [3]

No therapeutic advantage.

NOT ACCEPTABLE

The French Pharmacoeconomic Committee that assesses the medical benefit of new drugs and provides recommendations about reimbursement has downgraded its rating of the medical benefit provided by cholinesterase inhibitors (Aricept, Exelon, Reminyl*) and memantine (Ebixa*) in Alzheimer's disease from "major" to "low".

Avoiding harm. In early 2012 no treatment slowed the progression of Alzheimer's disease. Management of these patients is complex and relies mainly on psychosocial support aimed at maintaining independence and improving quality of life for both the patient and his or her caregivers.[4]

At best, drugs for Alzheimer's disease can only help to control behavioural disorders and stabilize or slightly improve cognitive function, in only a minority of patients.[5] It is therefore important not to cause further harm, especially by avoiding potentially serious adverse effects of cholinesterase inhibitors and memantine.

The adverse effects of cholinesterase inhibitors, due mainly to their cholinergic properties, include gastrointestinal disorders (sometimes significant vomiting), as well as neurological, psychiatric and cardiac disorders.[5] The main adverse effects of memantine are neuropsychological disorders, together with antimuscarinic and dopaminergic effects.[5]

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Escitalopram (Cipralex*): torsades de pointes [6]

Same problem as with citalopram (Celexa*).

NOTHING NEW

In late 2011, the British drug regulatory agency (MHRA) warned of a risk of torsades de pointes with escitalopram, a selective serotonin reuptake inhibitor antidepressant (SSRI). [7]

These disorders are also known to occur with citalopram [8], a racemic mixture of S and R citalopram. [9] Escitalopram, as its international non-proprietary name (INN) implies, is the S-enantiomer of citalopram. Patients taking citalopram are thus also taking escitalopram. Escitalopram has no proven advantages over citalopram in terms of antidepressant efficacy or adverse effects.

Gabapentin (Neurontin*) and pregabalin (Lyrica*): abuse and addiction [10]

NOT ACCEPTABLE

In Europe, in mid-2011, about 30 cases of dependence, abuse or withdrawal symptoms attributed to pregabalin had been reported to Swedish and French pharmacovigilance centres and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). About 20 cases of gabapentin addiction were published in detail.

The most frequestly reported disorders were withdrawal symptoms. More than half of the patients were hospitalized for withdrawal. Cases of excessive increases in the doses of gabapentin or pregabalin, unauthorized routes of administration, and combination with other substances were also reported.

In practice, it is better to avoid exposing patient to these risks when the expected benefits are not properly documented. Healthcare professionals should take care to prevent and detect addiction to pregabalin or gabapentin. When necessary, assistance with tapering off the medication should be offered.

Migraine attacks: acetaminophen** (Tylenol*) first [11]

About half of all patients with acute migraine obtain substantial relief after 2 hours with a single oral dose of acetaminophen 1000 mg.

OFFERS AN ADVANTAGE

A Cochrane Collaboration team reviewed available randomized clinical trials of adults with migraine. They identified 4 clinical trials that compared a single oral dose of acetaminophen 1000 mg versus placebo in a total of 1293 patients. [12] In these trials, no difference in adverse effects was observed between the two groups. [12]

In practice. More than one-third of migraine patients obtain relief with placebo. A single dose of acetaminophen 1000 mg is more effective. This treatment alone provides substantial relief in half of all patients, prevents recurrence and has no major adverse effects.

Varenicline (Champix*): aggression and homicidal ideation [13]

NOT ACCEPTABLE

Varenicline, a drug used for smoking cessation, carries a risk of neuro-psychological adverse effects, including depression and suicide.

Analysis of a series of detailed reports of aggression and homicidal ideation attributed to varenicline showed that most patients had no psychiatric history. These symptoms were often preceded by sleep disorders. Suicide and suicidal ideation were associated with signs of aggression in nearly one-third of cases. Aggressive symptoms recurred in patients who restarted varenicline.

In practice, it is better to avoid using varenicline for smoking cessation and to use nicotine replacement instead when drug therapy is considered necessary.

** Canadian Brand names added.*

*** Paracetamol, the generic name for acetaminophen in Europe, was used in the original.*

References

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