

## **Atypical Antipsychotic Drugs for the Treatment of BPSD in Subjects with Dementia**

Rosanna Erra

**School of Pharmacy, University of Salerno, Italy**

[ros.erra@libero.it](mailto:ros.erra@libero.it)

### **Summary**

Behavioural and psychological disorders in subjects diagnosed with Alzheimer's disease is one of the components that characterises the case history of dementia.

The availability of new antipsychotic drugs, so-called "atypical", has undoubtedly widened the therapeutic resources available. In recent times the scientific community has turned its attention to cardiovascular and cerebrovascular occurrences in patients affected with dementia and treated with atypical antipsychotic drugs. In 2006, the Italian Drug Agency (AIFA) deemed it necessary and urgent to define a drug control programme aimed at increasing awareness and giving updates regarding the use of such drugs. The doctor must compile a monitoring file for each patient at the beginning of the treatment with antipsychotic drugs and a follow-up file. These files must be sent to AIFA, which has set up a database of patients with dementia who are taking antipsychotic drugs. Furthermore, AIFA has identified the treatment plan that the doctors should follow before prescribing antipsychotics to patients with dementia.

**Keywords:** Behavioural and Psychological Symptoms of dementia, antipsychotic drugs in dementia.

### **Introduction**

The emergence of behavioural and psychological disorders in subjects diagnosed with Alzheimer's disease (BPSD), together with cognitive decline and functional loss, is one of the components that characterises the case history of dementia.

BPSD are the most common cause of institutionalisation of the patient, drug prescription and medical intervention and contribute significantly to a reduced quality of life of the patient and increased stress for the caregivers. Furthermore, the disorders are responsible for a considerable increase in costs for the illness linked to the need for hospitalisation and qualified care staff [4].

Therefore, their effect on the prognosis and the course of the dementia is considerable, at times superior, to that of cognitive decay [1-2].

BPSD include agitation (noisiness, wandering, walking aimlessly, sleep disturbance, and dressing/undressing), aggression (physical aggression, verbal aggression, aggressive resistance, destruction of objects and threats), psychosis (delusions, hallucinations and misidentifications) [3].

At present there are no approved drugs for the treatment of behavioural disorders or psychiatric symptoms associated with dementia.

Before the arrival of atypical antipsychotic drugs, typical neuroleptic drugs were the most used. The use of these drugs is limited at present because of frequent side effects, above all of the extrapyramidal type (parkinsonian tremors and disorders, motory restlessness, tardive dyskinesia), as well as drowsiness, low blood pressure (which increases the risk of falls) and antimuscarine effects (dryness of the mouth, constipation, urine retention) [4].

The availability of new antipsychotic drugs, so-called “atypical”, has undoubtedly widened the therapeutic resources available for the pharmacological treatment of BPSD in the elderly affected by dementia. On the other hand, the perception of an improvement in the benefit-risk balance compared to the traditional antipsychotic drugs, together with the need for efficient treatment, continues to promote the introduction of the atypical drugs in clinical practice (mainly risperidone, quetiapine and olanzapine) for the treatment of BPSD associated with Alzheimer’s disease, even though the results of clinical studies are still quite limited [5].

In recent times the scientific community has turned its attention to cardiovascular and cerebrovascular occurrences (stroke and TIA) in patients affected with dementia and treated with atypical antipsychotic drugs.

In 2004 the pharmaceutical companies reported a significantly higher occurrence of adversities of the cerebrovascular kind, compared to the placebo, in trials with olanzapine and risperidone carried out on elderly patients with BPSD. Following the reports, the regulatory bodies (FDA, EMEA, AIFA) issued specific recommendations for the use of these drugs. This led the regulatory authorities of several countries, including America and Italy, to establish that the use of olanzapine and risperidone in elderly people with behavioural disorders is *off-label*, that is, it is not one of the uses for which the drugs were approved (schizophrenia). These same precautions were also extended to two other principles belonging to the class of atypical antipsychotic drugs, quetiapine and aripiprazole [6].

If on the one hand such declarations pose many questions on the true effectiveness and benefits of atypical antipsychotic drugs, it must be pointed out that the use of these “*off-label*” drugs for the treatment of BPSD has remained a widespread procedure in all countries.

In fact, even though the drugs have not been approved by the authorities, they are the only suitable support in the control of BPSD where the use of other drugs have not produced improvements. [5-7]. We must bear mind that atypical antipsychotic drugs, not without side effects, must be administered correctly and appropriately, that is when the suitable conditions exist so that their use may result in a real advantage for the patient. To do this and to help the doctor decide, the Italian Drug Agency deemed it necessary and urgent to define a drug control programme aimed at increasing awareness and giving updates regarding the use of such drugs [8-9].

The Italian Drug Agency has above all stressed that, even though typical and atypical antipsychotics are not for the treatment of psychosis and/or behavioural disorders related to dementia, the doctor can, assuming full responsibility, use them in treatment should he/she believe that the patient cannot be treated effectively with other medicines as long as such a use is known and conforms to reports that have appeared in scientific publications (Act 94/98 art. 3).

In the abovementioned bulletin the Italian Drug Agency stated that the prescription of antipsychotic drugs for dementia can be carried out by the Authorised Specialist Centres appointed by each Region as experts in the diagnosis and cure of patients affected by dementia. The drugs are refundable on behalf of the National Health Service.

The doctor must compile a monitoring file for each patient at the beginning of the treatment with antipsychotic drugs and a follow-up file at each check-up (twice monthly).

The monitoring file contains: patient's personal details; diagnosis of the illness (Alzheimer's disease or other type of dementia); disorders and symptoms (delirium, hallucinations, aggressiveness or other symptoms); prescribed antipsychotic drug and relative posology (typical or atypical); attached copy of the patient's consent; other on-going therapies (antihypertensives, antiplatelets, anticoagulants, anti-diabetic drugs, statins, antiparkinsonian drugs).

In the follow-up file the doctor must state if the patient is continuing the on-going therapy and, if not, the reason for its suspension (inefficiency, extrapyramidal adverse reactions, cerebrovascular adverse reactions) or its substitution with a different antipsychotic drug.

The monitoring and follow-up files compiled by the doctor must be sent to the Italian Drug Agency, which has set up a database of patients with dementia who are taking antipsychotic drugs. Furthermore, the Italian Drug Agency has identified the treatment plan that the doctors should follow before prescribing antipsychotics to patients with dementia, underlining the following points:

1. Drug treatment of BPSD is to be undertaken only after excluding the fact that the behavioural disorders and the psychopathological manifestations are caused by an

underlying problem, for example the interaction of two drugs or the side effects of on-going treatment.

2. The doctors who prescribe the drugs must always assess the disorder to treat very carefully. In patients with dementia, in fact, not all behavioural disorders need to be treated with antipsychotics. In the first instance, if the symptoms are mild to moderate, it is best to ascertain if it is possible to reduce them by means of non-pharmacological treatment. There is in fact evidence from literature supporting the benefits of environmental interventions aimed at improving the quality of life and psychological well-being of subjects with dementia (for example organising the day according to a routine, stimulating socialisation, etc.).
3. Pharmacological treatment with antipsychotics must be reserved for the control of serious behaviour disorders (psychosis and/or invalidating agitation) that do not respond to non-pharmacological treatment, after assessing the cerebrovascular risks and the degree of impairment of the cognitive skills and after taking other concomitant pathologies into consideration.
4. Treatment with antipsychotics must start with a low dose and gradually increase until the clinically effective dose is reached.
5. If the treatment is ineffective, the drug must be gradually suspended and, if necessary, another compound taken into consideration.
6. If the treatment is effective, the doctor must continue to treat and monitor the patient for a period of 1-3 months and then, once the patient is asymptomatic, try to suspend the drug gradually. The high rates of placebo effect in all experiments carried out (around 40% on average) show that we are in the presence of symptoms that, by nature, fluctuate over time and that tend to work themselves out spontaneously in a short time.
7. Administration of two or more antipsychotics at the same time must be avoided.
8. The concomitant use of antipsychotics and tranquillizers/hypnotics, a factor associated with an increase in mortality, must be avoided.
9. Antipsychotics must be administered with extreme care to patients with cardiovascular risk factors after careful assessment of the clinical condition and a reassessment of the life parameters (and in particular blood pressure in clino and ortostatism) one week after beginning the therapy.

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