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Introduction of risperidone in the treatment of severe depressive episodes and drug-induced delirium in patient with somatic comorbidity

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Background:
The diagnostic process and course of treatment of a patient with psychiatric and physical comorbidity is also significantly affected by the specific reactivity of the patient to the applied medicines and requires very good knowledge of pharmacokinetics, pharmacodynamics and drug interaction, as well as close interdisciplinary cooperation. Atypical antipsychotics are best known as treatment of psychosis in schizophrenia and acute mania in bipolar disorder. However, these agents are increasingly being used to treat depression as well. This includes use as an augmenting agent to antidepressants drugs for patients with major depression who have inadequate responses to first-line monotherapy, i.e., for treatment-resistant unipolar depression. Finally, these agents are sometimes used as monotherapy for major depression, and for anxiety disorders such as GAD. Considering the existence of recommendations for introducing an atypical antipsychotic in the treatment of unipolar depression, in this case report we will demonstrate our experience relating to the effectiveness and good tolerability of risperidon in that indication. This case report is significant in various ways:

1. The treatment of depressive syptomatology and somatic comorbidity (HTA)
2. The treatment of drug-induced delirium, the consequences of interactions of psychiatric drugs and antihypertensives
3. The advantages of new antipsychotics: good effectiveness, better tolerability, fewer side effects and harmful interactions and greater combining possibilities – significant advantages compared to conventional psychiatric drugs.

Therapeutic resistance is the case when stable remission, or rather a satisfactory response to two different types of antidepressants applied in sufficient quantities for a sufficient period of time, has not been achieved. This includes at least one TCA and at least one SSRI.

Inadequate treatment response: is a weak therapeutic response which requires a change to the therapeutic plan or strategy (e.g. absence of at least 50% reduction in HAM-D), or in other words residual symptoms are still significant.

Adequate dose: oral does which is close to the highest dose recommended by the manufacturer.

Adequate length of treatment: at least four consecutive weeks of treatment, during which the patient is receiving adequate doses of medication for at least three weeks.

Remission: achieving a condition with no evident symptoms over at least two consecutive weeks (e.g. HAM-D < 7).

Delirium is an a acute reversible mental disorder characterised by disorientation and certain damage to consciousness, usually accompanied by emotional instability, hallucinations or illusions, as well as inappropriate, impulsive, illogical or violent behaviour.

Objective:
The objective of this paper was to investigate the effectiveness and tolerability of new therapeutic possibilities in the treatment of a therapeutically resistant severe depressive episode and drug-induced delirium caused by harmful drug interactions in female patients with somatic comorbidity**.**

Materials and method:
- Structured psychiatric interview, Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression scale (CGI-S, Item I, severity of disease)
- Neurological examination
- ECG, internist examination
- CT scan of the brain
- Hormonal status of the thyroid gland
- Expanded laboratory tests, mineralogram, urine analysis

Case report:
Patient Š.A. born 1950.g., divorced, retired, mother of two adult sons.
Family and personal medical history is without any outstanding characteristics. The subject is a 60 year old female patient, who has been mentally ill for many years (from 1987) and has been hospitalised a number of times with the following diagnosis: recurrent depressive disorder F 33.2, with somatic comorbidity: arterial hypertension grade III. Over a number of years of her illness, various antidepressants have been prescribed in combination with conventional antipsychotics, and the therapy has been modified several times. In spite of that, the achieved remissions were incomplete and lasted for a relatively short time.

Current illness:
The patient was received in the semiclosed ward because of deterioration in her mental condition which was manifested by a low mood, tearfulness, anxiety, loss of interest and motivation. She could not sleep, she had dark thoughts and a suicidal wishes. The patient's therapy consisted of levomepromazine 75mg/d, amitriptyline 125mg/d and Na-Valproat 900mg/d, as well as the following combination of antihypertensives: lisinopril 30mg/d and hydrochlorotiazid 25mg/d.

Psychological status upon admission:
Aware, oriented, with orderly appearance. Low mood, crying in interview, anxious. Verbal contact was established with attempted stimulation, replied with delay. Thought process formally orderly, talks about ideas of hopelessness, lack of prospects, meaninglessness of life. Confirms suicidal thoughts. Has hypobulia, anhedonia, sleep disturbance. Without hallucinations. HAM-D score = 34, CGI-S = 6.

Course of illness:
A couple of days after she was received, there was a rise in tension after which the internist modified the antihypertensive therapy and introduced a combination of enalapril 30 mg/d and hydrochlorothiazid 75 mg/d, with amlodipin 10mg/d, which the patient had not used before. Along with the existing therapy of psychiatric drugs, the patient started to complain about insecurity in walking, weakness, difficulty in speaking, but not in the sense of real dysarthria. In the following days she entered in a delirium, was upset, temporally disoriented, incoherent, with sight and hearing illusions (hallucinatory experiences).

The relevant diagnostics were carried out:
- Expanded laboratory tests, mineralogram, urine analysis within the limits of reference values
- Hormonal status of the thyreoid gland orderly
- ECG: findings orderly, internist examination : Dg: Arterial hypertension grade III
- Neurological examination orderly
- CT scan of the brain: signs of incipient atrophy of the cortex, other findings orderly

and delirium causes resulting from the general medical condition were ruled out.

We believe that a possible cause of the delirious conditions was an increase in psychotropic drugs which caused an intensification and summation of the anticholinergic activities of amitriptyline and levomepromazine. The increased concentration was probably caused by a reduced volume of circulating liquid which was caused by the potent antihypertensive therapy and/or was the consequence of an unwanted drug interaction and stronger binding of the newly introduced enalapril and amlodipine to plasma proteins than psychotrophic drugs. The antihipertensive therapy was modified (reduced dose of enalapril and hydrochlorotiazid, with the removal of amlodipina) and by substituting the psychiatric drugs and introducing risperidone 3 mg/d, with the existing stabiliser Na-Val 900 mg/d. The patient reacted favourably to the modified therapy, the delirious symtomatology subsided and depressive symptoms were also reduced. Two weeks after the introduction of risperidon the HAM-D score was 18, with excellent tolerability (orderly laboratory parameters). During further treatment and monitoring her condition improved further, depressive ideas fully withdrew and her mood stabilised, while her voluntary and instinctive dynamics increased and after 8 weeks the HAM-D-17 score was 5, and the CGI-S was 1, still without any side effects.

Conclusions:
A combined therapy with an atypical antipsychotic and mood stabiliser turned out to be effective and safe in the treatment of a resistant severe depressive episode, further complicated by a drug-induced delirium and somatic comorbidity.

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DRUG	METABOLISM		PROTEIN BINDING	EXCRETION	SIDE EFF./INTERACTION
	substrate	inhibitor			
Levomepromazine Methotrimeprazine	CYP 2D6	CYP2D6 (moderate)	90% or more	Renal and biliary	Tricyclic antidepressants: Concurrent use may produce increased toxicity or altered therapeutic response.
Amitriptyline	2D6 (major), CYP1A2 (minor), 2B6 (minor), 2C8/9 (minor), 2C19 (minor),	CYP1A2 (weak), 2C8/9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak)	Very highly protein bound (90% or more) in plasma and tissues	Urine (18% as unchanged drug); feces (small amounts)	Phenothiazines: Serum concentrations of some TCAs may be increased; in addition, TCAs may increase concentration of phenothiazines; monitor for altered clinical response
Valproate	(minor) of CYP2A6, 2B6, 2C8/9, 2C19, 2E1	**Inhibits** CYP2C8/9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak); **Induces** CYP2A6 (weak)	Protein binding (dose dependent): 80% to 90%	renal excretion after metabolism	Tricyclic antidepressants: Valproate may increase serum concentrations/adverse effects of some tricyclic antidepressants Phenothiazines: may increase valproic acid concentrations; monitor
Lisinopril + hydrochlorthiazide			Protein binding: <25% or Lisinopril does not appear to be bound to other serum proteins	Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine	
Enalapril + hydrochlorthiazide	CYP3A4 (major)		Protein binding: 50% to 60% or 20.1 to 89.1%	Excretion: Urine (60% to 80%); some feces	Prodrug, undergoes hepatic biotransformation to enalaprilat
Amlodipine	CYP3A4 (major);	CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8/9 (weak), 2D6 (weak), 3A4 (weak)	97.5%	renal excretion	
Risperidone	CYP2D6 (major) to 9-hydroxyrisperidone (similar pharmacological activity as risperidone), 3A4 (minor);	CYP2D6 (weak), 3A4 (weak)	Risperidone 90%; 9-hydroxyrisperidone: 77%	Urine (70%); feces (15%)	Valproic acid: Generalized edema has been reported as a consequence of concurrent therapy (case report)

No potential conflict of interest