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DIFFERENTIAL DIAGNOSIS OF PSYCHOTROPIC SIDE EFFECTS AND SYMPTOMS AND SIGNS OF PSYCHIATRIC DISORDERS

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SUMMARY

Diagnostic recognition and distinguishing of psychotropic side effects which are phenomenological Identical/similar to symptoms and/or signs of psychiatric disorders undergoing psychotropic treatment, is an integral element within the general diagnostic procedure. Unrecognising and undistinguishing of psychotropic-induced side effects from psychopathological phenomena and/or physical signs which are, according to relevant classification criteria, standard parts of psychiatric disorders, most frequently can cause increase the dose of the psychotropic medication, assigning of the unwarranted diagnoses, and/or addition of unnecessary medications. Some of the most frequent side effects that can be caused by the diagnostic difficulties and/or misjudgements of the phenomenological recognition and differentiating side effects from psychiatric symptoms and signs are: drug-induced akathisia, intensive anticholinergic pharmacodynamic effects including delirium, neuroleptic induced Parkinsonism, paradoxically antidepressants-induced worsening or re-emerging depression, acute dystonia and tardive dyskinesia and others. In conclusion, differential diagnosis of these side effects requires careful evaluation based on clinical experience and knowledge.

Key words: *psychotropic medication – side effect – psychopatological phenomena – physical sign – psychiatric disorder*

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INTRODUCTION

Modern clinical psychopharmacology and its applied component psychopharmacotherapy have achieved enormous progress in the treatment of psychiatric disorders, but it was not sufficient to prevent frequent relapses, new episodes of disorders, residual symptoms and signs, side-effects and very low level s of well-being, life-satisfaction and quality of life during pharma-cotherapy. Therefore, we can conclude that primary prevention of psychiatric disorders, which is considered to be the main goal of psycho-pharmacotherapy, is still relatively distant remote. Nevertheless, therapeutic possibilities of psycho-pharmacotherapy are significant, and they could be even greater if there is no limited phenomenon such as side-effects (Jakovljević 2007, Degrandpre 2006). According to the definition of World Health Organisation side-effect is: "Every effect of certain medication that is harmful, undesirable and that occurs on doses that are applied, according to the drug instruction, in prevention, diagnostic and treatment" (Lee and Rawlins 2004), and we can also defined it as: "Side effects are unwanted physical and emotional changes caused by drugs that usually have nothing to do with the drugs' ability to cure illnesses. No drug is specific enough to affect only the sick part of the body; all drugs do at least one thing more that we want them to do" (Gorman 2007). Since psychiatry and pharmaco-therapy inheriting and implement core ethical principle as classical and modern medicine which is "primum non nocere", it is obvious how significant is the influence of side-effects in psychopharmacotherapy and how important obstacle they can be in the implementation of the optimal therapeutic strategy. Hence, main challenge and goal in everyday clinical practice should be implementation of knowledge and skills that will enable how to do the least harm or to avoid harmful and unpleasant side-effects (Jakovljević 2009, Keshavan 1992, Healy 2005) and increasing levels of well being, life-satisfaction and quality of life, not only reduction and elimination of psychopathological symptoms and establishing remission (Jakovljević 2007, Jakovljević 2008, Stein 2008). To the previous

attitude about the adversity of side effects, which is explicitly pronounced in their definition, explanation that all side effects in every patient do not have to be harmful should be considered, and therefore opinion about absolute adversity may be doubtful. Certain side-effects, such as sedating and hypotensive influence of promazine can be useful in patients with sleep disorders and/or anxiety and/or hypotension, and increase in body weight as a side effect in the beginning or during the long term treatment of some recent antipsychotics can be desirable in thin patients (Gentle 2006, Alvarez-Jimenez et al. 2008, Usher et al. 2009).

CLASSIFICATION AND FREQUENCY OF SIDE-EFFECTS

Side-effects can occur after the administration of medication during the therapeutic process, especially when administered with herbal products that can also cause similar effects. However, side effects may occur when medication is implemented in preventive objectives as well as during the diagnostic procedure ex iuvantibus though standard medications are most often used in the diagnostic process, hence their side-effects are much more common (Lee & Rawlins 2004, Francetić & Huić 2007). Depending on the development mechanism, side-effects can be divided in two basic groups: A, B and C. Side-effects type A are characterised by the qualitatively standard, but quantitative augmented pharmacologic effects - dose dependent and predictable, type B side-effects are unexpected considering the pharmacological features of the medication, they are dose independent and unpredictable and type C, their phenomenological content is connected with higher frequency of defined disease during the administration of certain medication, mechanism of development is unknown, they have long latency and they are not experimentally repeatable (Lee & Rawlins 2004, Francetić & Huić 2007, Huić 2007).

Side-effects type A are for example abstinence syndrome developed following sudden discontinuation of benzodiazepines, cholinergic rebound and abstinence syndrome following sudden discontinuation of anticholinergics or antipsychotics with anticholinergic features such as chlorpromazine, clozapine and olanzapine, whereat clinical symptoms and abstinence signs are similar to the clinical features of flu (Woods et al. 1998, Ashton 2007, Lamber & Castle 2003, Liberman 2004).

Type B side-effects are for example myocarditis and hypersalivation that can be caused by clozapine, hyperglycaemia and diabetes caused by newer antipsychotics; suicidal risk, akathisia and aggression during the SIPS, agitation caused by benzodiazepines, acute myopathi, glaucoma, oligohidrosis, hyperthermia, and agitation that can occur during the topiramat treatment and agitation caused by gabapentine (Francetić & Huić 2007).

Table 1. Comparison of features type A and type B side effects

	Type A (augmented pharmacologic effects)	Type B (unexpected reactions)
Pharmacologic predictable	yes	no
Dose dependent	yes	no
Medication number dependent	yes	no
Drug interactions dependent	yes	no
Incidence	high	low
Morbidity	high	low
Mortality	low	high
Treatment	appropriation of medication dose	discontinuation of medication

There are some side-effects that can be classified according to DoTS method (Dose, Time-course, Susceptibility factors), which means that this method cab be used in order to classified side-effects according to the dose at which they commonly occur, time-course during which they occur and precipitated factors that make patient more receptive for certain side-effects.

1. Dose dependent side-effects are: toxic reaction occurring after the overdosing, collateral reaction occurring at standard therapeutic doses, and hypersusceptibility reactions that occur at subtherapeutic doses in receptive individuals.
2. Time-course related side effects are: time-independent reactions that can occur at any

phase of the therapeutic process; time-dependent reactions: occur immediately after the drug initiation, not necessarily after and reactions that occur when a drug is administered too rapidly; reactions that occur early in the therapeutic process then they tend to disappear during the treatment; reactions that occur after some delay but with less risk during longer term therapy; late reactions that are characterise with increase risk of developing after the repeated exposure; withdrawal reactions after the discontinuation or reduction of the previously initiated long term treatment; delayed reactions that occur with some latency time.

3. Susceptibility factors: genetic, age, gender, ethnic group, physiological variation, exogenous factors (smoking, drug-drug or drug-food interaction, psychoactive substances) and diseases (Aronson 2009, Lawson 2000).

In primary health care approximately 2% of patients receiving pharmacotherapy develop side-effects, hence in hospitalised patients this percentage is even higher. 2.5-8.4% of all hospitalizations was because of the side-effects. Mortality related to side effects 0,0,1-0,1% (Lee & Rawlins 2004, Francetić & Huić 2007). During the year 2008. there were 1680 reported side effects of drugs and medical products which is 20% more than the previous year. Antipsychotics are on the third place within the number of reported side-effects mentioned above (Anonimno 2009).

SIDE-EFFECTS OF PSYCHOPHARMACOTHERAPY AND PSYCHIATRIC DISORDERS THAT CAN BE RELATED WITH THE DIFFERENTIAL-DIAGNOSTIC DIFFICULTIES

Factors that have positive influence on validity and reliability of the differential-diagnostic procedure between side-effects of psychopharmacotherapy and symptoms and signs of psychiatric disorders are knowledge and clinical experience of the psychiatrist and as much as possible lesser psychiatrist's subjectivity in differential-diagnostic procedure, and patient's cooperability and as much as possible greater spontaneity and subjectivity in side-effect description (Sussman 2005, Preston et al. 2007).

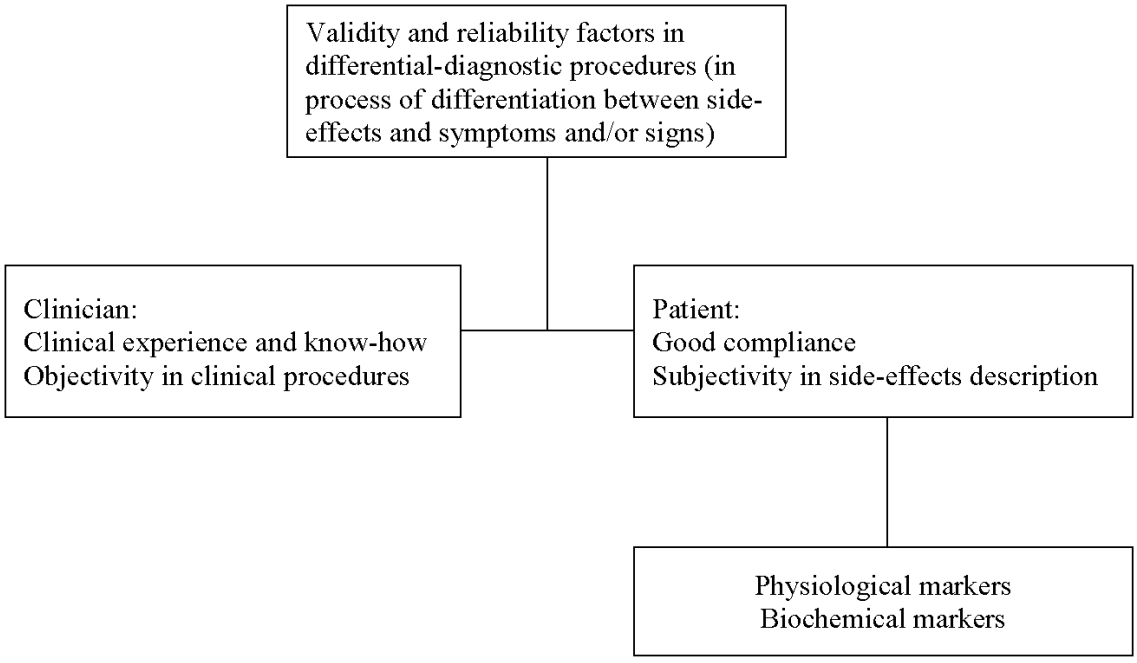

Figure 1. Factors that have positive influence on validity and reliability of the differential-diagnostic procedure

Sometimes even experienced psychiatrist can perceive difficulties during the differential-diagnostic procedure between side-effects of psychopharmacotherapy and symptoms and signs of certain psychiatric disorders, and most common consequences of full or partial undistinguishing could be:

1. exception of the medication that is necessary in the treatment;

2. introduction of the medication that is unnecessary in the treatment;
3. increasing the dose of the medication that caused the (unrecognised) side-effect;
4. decreasing the dose of the medication that didn't cause (unrecognised) side-effect;
5. misdiagnosing;
6. negative influence on patient's compliance as well as additional stigmatisation (Sussman 2005, Preston et al. 2007, Hudson et al. 2004, Novak et al. 2009).

Clinical features of akathisia can be very similar to clinical features of agitation in anxiety disorder when anxiety intensifies to the level of agitation and to the clinical features of the exacerbation of psychotic disorder. Akathisia is much more frequent in younger individuals, following the administration of highly potent antipsychotics, at the beginning of psychopharmacotherapy or after a few weeks, but it can also develop during the treatment that does not include antipsychotics (such as SSRIs and TCAs). Unrecognizing of acathisia can result with initiation of antipsychotic or increasing antipsychotic dose. Diagnosis can be established also ex iuvantibus by introducing anticholinergics in the treatment which will reduce the intensity of akathisia symptoms and signs (Usher 2009, Preston et al. 2007).

In clinical practice difficulties in differential diagnosis can be produced by distinguishing anticholinergic delirium and psychotic disorder. But, acute appearance primary organic symptom s such as confusion, disorientation, tactile and visual hallucinations together with the mydriasis, accelerated pulse and dryness of mucous membranes and information about taking anticholinergics en elderly patients indicate that it is most probably anticholinergic delirium (Liberman 2004, Preston et al. 2007).

Medication induced parkinsonism can be presented with mild hypokinesia, slow speech, reduced or absent facial expression, tremor and muscle rigidity, which in combination with apathy, social isolation of the patient can cause symptoms very similar to depression (Uzun et al. 2005, Preston et al. 2007).

Increase of depressive symptoms or relapse of depressive disorder in patients taking antidepressive pharmacotherapy are most frequently related with the inappropriate antidepressant, inadequate antidepressive dose or inadequate patient's compliance. Nevertheless, toxic influence of antidepressants on central nervous system can result in confusion, memory disorder, anxiety, irritability and agitation which diagnostically should be differentiated from the increase of depressive symptoms or relapse of depressive disorder as it is mentioned above. Physiological signs of antidepressant toxicity can be very helpful in differential diagnosis, as well as determining blood level of antidepressants (Gorman 2007, Preston et al. 2007).

Some patients that are more than six months on selective serotonin reuptake inhibitors can develop symptoms such as apathy, lack of motivation and emotional blunt presented as inability to cry. According to one hypothesis, long term high level of serotonin in CNS progressively inhibit dopamine neurones in frontal cortex especially considering the fact serotonin receptors were found on the cell bodies of dopamine neurons. Thereby we can explain emotional disinhibition that sometimes occurs during the long term treatment with SSRIs. These psychopathologic symptoms should be distinguished from the symptoms of primary depressive disorder, and clinical experience shows that these symptoms tend to reduce after discontinuation of SSRIs or after administration of dopamine agonists such as bupropione (Preston et al. 2007, Hoehn-Saric et al. 1990, Barnhart et al. 2004).

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