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SUICIDALITY AND SIDE EFFECTS OF ANTIDEPRESSANTS AND ANTIPSYCHOTICS

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SUMMARY

Antidepressants and antipsychotics can cause side effects in various organs and organic systems, and some (and) in the central nervous system, which can also be clinically manifested by suicidal behavior as well. Tricyclic antidepressants particularly of imipramine and clomipramine can have pro-suicidal effect, which is believed to be the consequence of their own hypothetic asynchronous cognitive-psychomotor pharmacodynamic action. Antidepressants from the group of selective serotonin reuptake inhibitors can at the beginning of administration as monotherapy also have pro-suicidal effects in patients with hints of suicidality or suicidal behavior, by increasing the intensity of already present suicidal predictors, such as dysphoria, anxiety, impulsiveness, agitation etc. Antipsychotics can act stimulatingly upon predictors of suicidal behavior, that is, pro-suicidal in an indirect way through side effects they cause indirect pro-suicidal neurological and consecutive psychological impact, as it is called. It is particularly valid for classic antipsychotics causing primarily neurological, i.e. extrapyramidal side effects, along which consecutive psychological side effects can occur as well. However, new antipsychotics in comparison to classic ones, have less pronounced neurological, extrapyramidal symptoms and signs but more somatic-metabolic side effects, and thereby their action can be mostly manifested as indirect pro-suicidal neurological and somatic-metabolic as well as consecutive psychological activity.

Key words: *antidepressants and antipsychotic medication - side effect – suicidal behavior*

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INTRODUCTION

Side effect is unwanted and undesirable physical, emotional, and/or behavioral effect of a medication that may be unrelated to its therapeutic effects. It is essential to distinguish between the side effect of a drug and allergic reactions to it, whereas side effect is caused by the physiological and pharmacological actions of the medicine (Ayd 2000). Psychopharmaca cause side effects in many organs and organic systems, and some (and) in the central nervous system, what can also be manifested by suicidal behavior and suicidality respectively, as this psychopathological phenomenon is called as well (Aronson 2009). Suicidal behavior is defined as a notion encompassing a broad meaning, from suicidal ideas, their verbalization and intent to suicide attempts and committed suicide. It is conscious and unconscious, intentional and unintentional, actual and prolonged, and continuously aimed at self-destruction (De Leo et al. 2006). The outcome of suicidal behavior depends on many factors of suicidal risk, what in the broadest sense includes mental and somatic disorders and illnesses, as well as psychosocial and demographic components (Marčinko 2008, Manoranjitham et al. 2010). Certain factors of suicidal risk are: elderly, male, social/life events – bereavement, unemployment; chronic somatic illness (pain, terminal states), recent inpatient psychiatric treatment, previous suicidal attempts, actual suicidal thoughts, intents and plans; psychiatric disorders as affective disorders, psychotic disorders, anxious disorders, alcoholism and other addictions and personality disorders especially borderline disorder; and psychiatric symptoms such as depressiveness, intensive anxiety, panic attacks, hopelessness, command hallucinations, impulsivity, aggressivety, severe anhedonia, dysphoria, agitivity, shame or humiliation, decreased self-esteem, loneliness, violence toward others, anger, self-harming behaviors, insomnia; as well as side effects of psychopharmaca akathisia, tardive dyskinesia and direct and/or indirect pro-suicidal action of some antidepressants and antipsychotics (see Table 1) (Kutcher & Chehil 2007, Fawcett et al. 2009).

GENERAL PRINCIPLES OF PRO-SUICIDAL ACTION OF ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Antidepressants and antipsychotics, depending on the classification group to which they belong and clinical picture/nosologic unit of patients they are prescribed to, can in various ways directly or indirectly act pro-suicidally, and, respectively, influenced on the predictors of suicidal behavior (see Table 2).

Table 1. Factors of suicide risk

Factors of suicide risk
elderly
male
social/life events – bereavement, unemployment
chronic somatic illness (pain, terminal states)
recent inpatient psychiatric treatment
previous suicidal attempts
actual suicidal thoughts, intents and plans
psychiatric disorders: affective disorders, psychotic disorders, anxious disorders, alcoholism and other addictions and personality disorders
psychiatric symptoms: depressiveness, intensive anxiety, panic attacks, hopelessness, command hallucinations, impulsivity, aggressivety, severe anhedonia, dysphoria, agitivity, shame or humiliation, decreased self-esteem, loneliness, violence toward others, anger, self-harming behaviors, insomnia
side effects of psychopharmaca: akathisia, tardive dyskinesia, direct and/or indirect pro-suicidal action of some antidepressants and antipsychotics

Table 2. Types of pro-suicidal impact of antidepressants and antipsychotics

1.	Intensifying pro-suicidal activity
2.	Hypothetic asynchronous cognitive-psychomotor effect
3.	Indirect pro-suicidal neurological and consecutive psychological effect
4.	Indirect neurological and somatic-metabolic, and consecutive psychological activity
5.	Iatrogenic pro-suicidal activity

Antidepressants from the group of selective serotonin reuptake inhibitors (SSRIs) can at the beginning of administration as monotherapy also have pro-suicidal effects in patients with hints of suicidality or suicidal behavior, by increasing the intensity of already present suicidal predictors, as are dysphoria, anxiety, impulsiveness, aggressivety, agitation, etc.

In clinical practice, after a certain time from the onset of application of the first antidepressants in the narrower sense, i.e. tricyclic antidepressants (TCAs), particularly of imipramine and clomipramine (the so-called thymoleptics), experience has shown that some patients in the treatment phase in which clinical picture as a whole gives impression of improvement and advancement towards remission, do commit suicide. Phenomenologically, i.e. according to clinical picture, that is paradoxical, but the reasons can perhaps be sought in dichotomy between clinical picture and intrapsychic pathological contents. Thus, in this "classical" and long gone age of antidepressant psychopharmacotherapy it has been supposed that the cause is perhaps in hypothetic asynchronous cognitive-psychomotor therapeutic activity. Namely, antidepressants cause psychomotor activation and dynamization in a patient, what creates the possibility for depressive cognitive contents in the shape of suicidal thoughts on which antidepressants hypothetically act therapeutically more slowly than on psychomotor inhibition, which are then realized by committed suicide. Here, in the current conceptual and terminological context, psychomotor activation and disinhibition of a patient as the result of therapeutic activity of the mentioned antidepressants, could be to an extent compared to, e.g. impulsiveness and aggressivity as predictors of suicidal behavior as they are understood and classified today (Varagić & Vrhovac 1985, Preston et al. 2008). Contemporary understanding and explanation of these phenomena generally match with the previously mentioned hypothesis. Slower therapeutic effect on suicidal thoughts may psychologicaly effect in return on the patient in a way to demoralize him. If in that initial phase of treatment effects and side effects of antidepressants such as agitation and restlessness, and if even interpolates with life events, suicidal thoughts can be intensified before the full therapeutic respond. Therefore, but rarely, some patients may become temporarily more suicidal after the commencement of treatment and reasons for this may be very different (Labbate et al. 2010).

Antipsychotics in the first place, but also some antidepressants, can act stimulatingly upon predictors of suicidal behavior, that is, pro-suicidally and in an indirect way through side effects they cause indirect pro-suicidal neurological and consecutive psychological impact, as it is called. It is particularly valid for classic antipsychotics causing primarily neurological, i.e. extrapyramidal side effects, along which consecutive psychological side effects can occur as well. However, new antipsychotics in comparison to classic ones, have less pronounced neurological, extrapyramidal symptoms and signs, but more somatic-metabolic side effects. As the type of pro-suicidal activity in them can be mostly manifested indirect pro-suicidal neurological and somatic-metabolic, as well as consecutive psychological activity (Jakovljević 2001, 2009).

Pro-suicidal activity of antidepressants can also be iatrogenic, in a concrete example the consequence of a mistake in diagnostic procedure. Namely, the recognition of bipolar affective disorder II (BAP II) is a complex differential diagnostic procedure and a great professional challenge for every psychiatrist, requiring substantial clinical knowledge and experience. That this is really so, proves clinical practice in which BAP II is often mistakenly diagnosed as unipolar depression or borderline personality disorder. As regards the timely identification of suicidal potential in a patient, it is more important to recognize mixed dysphoric mania. Exactly here errors often happen, and it is wrongly diagnosed as agitated unipolar depression, what determines inadequate therapeutic approach. In accordance with the later diagnosis, SSRIs are prescribed. As they intensify psychomotor agitation, which is the predictor of suicidal behavior, this mistake logically increases suicidal risk. Therefore, mood stabilizers should be introduced in therapy as drugs of the first choice instead of SSRIs. Furthermore, some clinicians believe that, as in rapid cycling, one of the best ways to address mixed states, besides introducing mood stabilizers, is to begin by gradually withdrawing the antidepressant (Benazzi 2007, Perlis et al. 2009, Schneck 2009, Benazzi 2010).

ANTIDEPRESSANTS

Selective serotonin reuptake inhibitors

In the latest decade of the 20th century several articles were published with conflicting data from the clinical therapeutic trials whether the SSRIs antidepressants can induce suicidal thoughts and/or suicidal behavior with respect to their ability to have pro-suicidal action as adverse effect. 1990. was published an article with 6 patients diagnosed as depression, who developed sudden, violent suicidal thoughts during the treatment with fluoxetine without previously registered suicide attempt (Teicher et al. 1990). Two years thereafter was published article describing similar founding in patients treated with sertraline (Balon 1993). These, and consequent data, made significant contribution in creation speculations about SSRIs antidepressants as "suicide pills", which resulted with a significant decrease in antidepressants prescriptions in the USA from 2003 to 2005 (Schatzberg et al. 2007). Following investigations failed to show association between fluoxetine and suicidality comparing with other antidepressants (Fava & Rosenbaum 1991). Study with patients treated with tricyclic antidepressant imipramine, placebo and fluoxetine, showed that more suicidal thoughts were registered in groups treated with imipramine and placebo, comparing to the group treated with fluoxetine (Beasley & Dornseif et al. 1991). Former suggests that treatment-emergent suicidal thoughts can be explained as a symptom of underlying depression rather than as a result of the medication. But as is well known fluoxetine can also provoke agitation or perhaps akathisia-like side effects, and it can be logically concluded that some depressed patients can become more suicidal after these side effects occur (Rothschild & Locke 1991). Subsequent studies to the black box warning focused on the risk of suicidal behavior with antidepressant use failed to show any association (Hammad et al. 2006). Another study showed that the risk of suicide attempts was highest in the months prior to antidepressants therapy (Simon et al. 2006). FDA-initiated study included 100,000 patients found a 2 % risk of newly developed suicidal like behavior in patients age 18-25 versus 1 % in placebo group. However there is a small group of patients with latent bipolar disorder, those developed agitation while taking antidepressants and patients who became sufficiently recovered to act on suicidal impulses before significant mood improvement (Schatzberg et al. 2007).

In SSRIs antidepressants, pro suicidal activity is represented as intensifying pro-suicidal activity and, more theoretically than qualitatively significant, also as the type of indirect pro-suicidal neurological and consecutive psychological activity (see Table 3).

Table 3. Types of pro-suicidal activity in antidepressants and antipsychotics

SSRIs	Intensifying pro-suicidal activity Iatrogenic pro-suicidal activity Indirect neurological and consecutive psychological activity
TCAs	Hypothetic asynchronous cognitive-psychomotor activity Indirect neurological and consecutive psychological activity
Classic antipsychotics	Indirect neurological and consecutive psychological activity
New antipsychotics	Indirect neurological and somatic-metabolic, and consecutive psychological activity

Tricyclic antidepressants

Tricyclic antidepressants, particularly the so-called thymoleptics, primarily imipramine and clomipramine, can act pro-suicidally, mainly according to hypothetical type of asynchronous cognitive-psychomotor activity (Varagić & Vrhovac 1985, Preston et al. 2008, Labbate 2010). Much less significantly they act through the type of indirect pro-suicidal neurological or other effect, and consecutive psychological impact, because side effects that they cause are transient as a rule (Cole & Bodkin 1990, Aronson 2009). There are suggestion that amitryptiline and tetracyclic maprotiline may disinhibit some individuals who then become aggressive and attempt suicide (Montgomery 1997). In tricyclic antidepressants, manifested cardiac side effects can be life threatening in overdosage (Glassman et al. 1993). Thus, in packages special preventive quantitative measures are performed to prevent patients the access to the quantity which could be abused for committing suicide.

ANTIPSYCHOTICS

Classic antipsychotics

Classic antipsychotics act through indirect pro-suicidal neurological and consecutive psychological effect. Neurological side effects are extrapyramidal symptoms and signs. Among them is regarding their indirect pro-suicidal activity in the first place akathisia followed by much rarer tardive dyskinesia (Sandyk & Kay 1991). Akathisia is, besides motor agitation, also accompanied by emotionally very unpleasant anxiety and/or frustration and irritable mood and dysphoria respectively. Suicidal tendencies can develop in psychotic patients in whom the application of classic antipsychotics caused akathisia. However, newer data show that affective symptoms need not occur or aggravate if new antipsychotics are administered (Aronson 2009, Kasantikul 1998, Leong & Arturo Silva 2003).

Dysphoria, which might be caused by antipsychotics is often an unrecognized side effect which untowardly effects motivation of the patients for taking medications. If it lasts for a longer time, suicidality may appear. Antipsychotics can cause depression-like syndrome with suicidality, and that syndrome must be diagnostically differentiated from induced akinesia. Affective symptoms in clinical picture are as a rule related to suicidal behavior, and as antipsychotics can induce major depressive episode, they can in this way act pro-suicidally as well (King et al. 1995, Tollefson et al. 1998, Voruganti & Awad 2004).

Haloperidol, fluphenazine and pimozide are highly potent antipsychotics because they belong to the strongest dopamine receptors blockers, and due to that have the highest potential for causing extrapyramidal side effects and also for pro-suicidal activity in the sense of indirect neurological and consecutive psychological effect (Aronson 2009, Schatzberg et al. 2007).

New antipsychotics

Clozapine is the only antipsychotic for which antisuicidal activity has been proven, while for other new antipsychotics is supposed that they lessen the risk for suicide in schizophrenic patients (Reinstein et al. 2002, Meltzer et al. 2004). But despite that, exceptions of this general feature of new antipsychotics have been described. Namely, at the beginning of treatment with aripiprazole in some patients emerged suicidal thoughts and suicidal attempts, while it also caused dysphoria and agitation, what is markedly expressed if it is applied in adults along with antidepressants (Ketter & Wang 2010). Quetiapine can also act pro-suicidally, particularly if administered in adults who are taking antidepressants (Altamura et al. 2003, Ketter & Wang 2010). In new antipsychotics, as the type of pro-suicidal activity primarily can be manifested indirect pro-suicidal neurological and somatic-metabolic, as well as consecutive psychological activity (Aronson 2009, Jakovljević 2001, 2009).

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