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Mania induced by antidepressants – characteristics and specific phenomena in children and adolescents

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Summary

The phenomenon of drug-induced mania, i.e., a manic episode associated with the use of pharmacotherapy (in particular antidepressants) is well defined and described in groups of adult patients. The negative effect on the course of bipolar disorder has been confirmed. In the group of children and adolescents, this subject is still poorly known and rarely described because of controversies in diagnosing early-onset bipolar disorder. The authors present an overview of current research on this problem starting from case reports, through open studies to randomized trials. Because the results of studies are ambiguous, the main problems that hinder the formulation of objective conclusions and the most important directions for further research are also discussed. The authors also present current hypotheses on the phenomenon of drug-induced mania in children and adolescents to systematize knowledge on the subject and provide diagnostic help in everyday clinical work. In a group of children and adolescents, there is a need to differentiate the phenomenon of drug-induced mania depending on the basic disorder, because similarly to studies that concern adult patients this problem seems to occur more frequently in patients with bipolar disorder than in other psychiatric disorders. It seems that the diagnosis of drug-induced mania is possible in children and adolescents at the present stage of knowledge, however, the assessment of the prevalence of this phenomenon requires careful evaluation in further studies.

Key words: mania, antidepressant agents, adolescent

Introduction

The problem of drug-induced affective episodes such as mania, hypomania, or mixed episodes is not fully categorized. According to the diagnostic criteria of DSM IV-TR [1], the occurrence of substance-induced affective episode precluded the diagnosis of bipolar disorder. However, in the current DSM-V classification [2], apart from the separate category "Substance/medication-induced bipolar and related disorder", it

is possible to diagnose bipolar disorder if a patient presents with a full-blown episode of pharmacologically-induced mania or hypomania beyond the biological action of the drug. The authors of DSM-V emphasize that the diagnosis should be made with caution and taking into account the fact that single symptoms of mania, such as dysphoria or agitation, may be a side effect of the antidepressant treatment itself [3].

At the present stage of knowledge, in the adult population with bipolar disorder the negative effects of antidepressants on the induction of manic episodes, frequent relapses and a tendency to change the course of the illness in a continuous, chronic course without periods of normothymia, is confirmed [4]. This negative influence can also be observed even when antidepressants are used in patients treated with mood stabilizers [5].

In the adult population of patients with unipolar affective disorder, the incidence of manic episode or hypomania is estimated at 8–20% [6, 7]. In many current publications authors compare groups of patients with unipolar affective disorder with no history of drug-induced mania with groups of patients with a history of drug-induced episodes and groups of patients with bipolar disorder. It turns out that in variables such as: family history of bipolar disorder, presence of atypical symptoms of depression, early onset of unipolar disorder (< 30 years), comorbidity of anxiety symptoms, borderline personality disorder, number of suicide attempts, patients with unipolar affective disorder are significantly different from patients with unipolar affective disorder with an episode of pharmacologically-induced mania. In contrast, patients with a history of drug-induced mania are similar to the group of patients with bipolar disorder. Therefore, authors suggest to classify this group of patients as the group of patients with a diagnosis of bipolar disorder or bipolar disorder "not otherwise specified" (NOS). The episodes of drug-induced mania or agitation in patients with a positive family history or above-mentioned features are considered by some authors to be the BD predictors [8]. We also find similar opinions in Polish studies, for example, in the conclusions from the TRES-DEP study [9]

Specificity of the drug-induced mania phenomenon in children and adolescents

The above observations resulted in the problem of pharmacologically-induced mania becoming an important area of research in the population of children and adolescents. In the last decade, there was a tremendous increase in the use of antidepressants, especially SSRIs, in a population of children and adolescents. In the years 1987–1996 in the United States, a threefold increase in the use of these medicines in children and sevenfold increase in a group of adolescents was observed, and the trend continues to this day This is undoubtedly associated with increased recognition of affective disorders in this group of patients. Also the number of studies on the incidence and severity of adverse effects increased, including the risks associated with the impact of drug treatment on the induction of manic episodes.

Particularly important problem in the group of children and adolescents is the differentiation between drug-induced mania and symptoms described as a group of behavioral side effects (mainly excessive activation) associated with the use of SSRIs

(activation cluster adverse events AC-AEs) [10]. Activation cluster adverse events are characterized by increased mobility, excitation, agitation, excessive impulsiveness, not feeling the need to rest, sleep disturbances in the absence of changes in mood and other symptoms of mania. According to some authors, the occurrence of activation symptoms, especially in the youngest patients with a family history of affective disorders, should be treated as a risk factor for bipolar disorder [11]

Review of studies on drug-induced mania in children and adolescents

Case studies

Joseph et al. [12] conducted a meta-analysis of case reports of mania induced by antidepressants in children and adolescents including 5 cases of mania induced by citalopram, 11 – by fluoxetine, 7 – by paroxetine, 5 – by sertraline, 1 – by venlafaxine. Median time to onset of manic episode was 21 days (2–365 days), the duration of episodes was usually less than 8 weeks, although in four cases, the symptoms have been present for a long period of time (5–12 months). The patients were observed for 2–52 weeks, with an average of 20 weeks. 21% of patients had a family history of bipolar disorder, while 45% showed no family history of affective disorders. The most common interventions included: reduction of the dose of the antidepressant (59%), use of additional mood stabilizer (38%). After dose reduction or complete withdrawal of the drug, the majority of patients obtained a general improvement.

Isolated cases of mania induced by antidepressants are also described in patients with other psychiatric disorders: obsessive-compulsive disorder (OCD) [13–15] or anxiety disorders [16]. In the literature one can also find the descriptions of mania induced by other substances than antidepressants: methylphenidate [17] and atomoxetine [18], which are used in the treatment of ADHD. However, these observations are not confirmed in studies on larger groups. For example, in the study conducted by Waxmonsky et al. [19] 106 children aged 5–12 were divided into two groups: (1) patients with ADHD and (2) patients with so-called severe mood dysregulation (SMD), described by Ellen Leibenluft [20–23]. Both groups were treated equally with methylphenidate. In both groups, pharmacotherapy proved to be effective, had an impact on functioning improvement, including a reduction in mood symptoms measured by the YMRS (*Young Mania Rating Scale*). Similarly, in the study by Dell'Angello et al. [24], there were no statistically significant differences in the occurrence of mania between children receiving atomoxetine and placebo.

The influence of pharmacotherapy on the course of bipolar disorder tested in larger groups of young patients

In the study by DelBello et al. [25], 71 adolescents with bipolar disorder hospitalized with manic or mixed episode were observed for a period of 12 months from the date of discharge. The study showed a significant reduction in the remission period between affective episodes in patients treated with antidepressants. In the study conducted by

Faedda et al. [26], including 69 patients with bipolar disorder, drug-induced manic episode was observed in half of the patients (35 patients). Most of them (25 patients) were treated with antidepressants (particularly the SSRIs), 8 patients were treated with psychostimulants, 1 patient – with corticosteroid, and 1 – with carbamazepine. Baumer et al. [27] published data derived from observations of a group of 52 children and adolescents with bipolar disorder, or risk defined as the occurrence of this disorder in one parent, over the average period of 1.4 years. In half of them, deterioration of the course of the current affective episode or induction of a manic episode was observed after the use of antidepressants (80% in the SSRI group). Also Biedermann et al. [28] described three times higher incidence of manic episode in patients with bipolar disorder treated with antidepressants (SSRIs) compared with patients not treated with SSRIs.

There are also studies where lack of effect of pharmacotherapy on the course of bipolar disorder in children and adolescents was proved. In the study conducted by Soutullo et al. [29], adolescents hospitalized for bipolar disorder were interviewed on the experience of previous pharmacotherapy, especially with antidepressants. It was then verified on the basis of the available data from the medical history of the patient. The study demonstrated no adverse effect of antidepressant treatment on the course of bipolar disorder. Similar conclusions can be drawn from the study by Pagano et al. [30] conducted in the group of outpatients. However, the work of DelBello [31] indicated that in patients with a history of psychotic depression receiving antidepressants manic episodes were observed four times less frequently than in the control group during the 2-year follow-up period.

The effect of pharmacotherapy on the induction of manic episodes in patients treated for mental disorders other than bipolar disorder

In the study by Wilens et al. [32], in a group of 82 patients treated with SSRIs for unipolar disorder or obsessive-compulsive syndrome (OCD), an episode of drug-induced mania was observed in 6% of patients. A pharmacoepidemiological study conducted by Martin et al. [33] was designed to evaluate the susceptibility to induction of manic episode depending on patient's age. The study group consisted of 87,920 outpatients diagnosed with anxiety disorders and affective disorders. Patients with the diagnosis of bipolar disorder were excluded from the study. Patients were divided into 3 age groups: 5–10 years, 10–14 and 14–29 years. Subjects were observed for a period of 41 weeks on average. In 5.4 % of patients, manic episode was observed, and in half of those patients manic episode occurred after using antidepressants (SSRIs). Contrary to previous hypotheses, the group of 10–14 year-olds turned out to be the most vulnerable to the occurrence of drug-induced manic episode.

To summarize, it seems that in a group of children and adolescents, there is a need to differentiate the phenomenon of drug-induced mania depending on the basic disorder because, as in the studies that concern adults, drug-induced mania seems to occur more frequently in patients with bipolar disorder than in other psychiatric disorders. Furthermore, despite the divergence in result, it seems that the diagnosis of drug-induced mania is possible in children and adolescents at the present stage of

knowledge, however, the assessment of the prevalence of this phenomenon requires careful evaluation in further studies.

Clinical trials

Clinical trials assessing the effectiveness of pharmacotherapy with antidepressants in children and adolescents are an important source of knowledge on the subject of interest. Due to the nature of the studies (randomization, double-blind trial, adequate control group), published data seem to be valuable and conclusions seem to be the most objective. These studies also include indirect information on the induction of manic episodes because they are often included in the group of side effects. In some studies, manic symptoms were assessed in questionnaires assessing the severity of side effects, in others they were reported spontaneously by patients or researchers.

The largest number of studies concerned the assessment of the efficacy of fluoxetine in the treatment of children and adolescents. Fluoxetine is also one of the few SSRIs approved by the FDA (Food and Drug Administration) for the treatment of depressive episodes in this age group. The TADS (Treatment of Adolescent Depression Study) [34, 35] concerned adolescent outpatients with moderate or severe depressive episode. Drug-induced manic episodes were observed in 4 (3.67%) patients from the fluoxetine only group, in 1 (0.93%) patient from fluoxetine and cognitive behavioral psychotherapy (CBT) group, in 1 patient (0.93%) from the placebo group, and none of patients from a group receiving CBT only. In studies conducted by Emslie et al. [36], which concerned children and adolescents treated for depressive symptoms, drug-induced manic episode was observed in 6.25% of patients treated with fluoxetine compared with 2% in the placebo group. In contrast, in a similar study of this group from 2002, it was 0.92% in the treated group and 0% in the placebo group, respectively (statistically insignificant difference) [37].

In most of clinical trials evaluating the efficacy of other antidepressants, the induced manic episode is not included in adverse event reports, but only described after a spontaneous occurrence. In the study on the effectiveness of fluvoxamine [38] or paroxetine [39] in patients with anxiety disorders, there was no information about drug-induced manic episodes. In studies evaluating treatment of depression with SSRIs: sertraline [40–42] – drug-induced mania was not reported, escitalopram – 1 patient in the placebo group [43], venlafaxine [44] (the TORDIA study – Treatment of SSRI-Resistant Depression in Adolescents) – only 1 case of drug-induced mania was documented.

However, there are also studies that have shown a relationship between pharmacotherapy and the much more frequent induction of manic episode – e.g., Shirazi et al. [45] reported manic symptoms in 16.7 % of patients with major depressive disorder (MDD) treated with citalopram.

Basic inconsistencies that make it difficult to draw specific conclusions and set directions for further research in the field of interest are complex, and include the following:

- limited number of research;
- the risk of ‘research bias’;

- differences in defining a manic episode, use of different diagnostic criteria in clinical trials;
- reporting the phenomenon of drug-induced mania based on spontaneous reports of patients, rather than a formal recognition;
- comparing studies of patients with different psychiatric disorders (it appears that a lower percentage of drug-induced mania is observed in studies of patients treated for conditions other than affective disorders – therefore, a separate analysis of the phenomenon of drug-induced mania in patients with bipolar disorder and in patients taking antidepressants for other reasons should be conducted. It is possible that the etiology of this phenomenon is not the same in those groups);
- differences in the group selection criteria in studies of patients with unipolar affective disorder (however, there are studies that use tools to differentiate bipolar disorder from unipolar disorder, such as excluding patients with a history suggesting a risk of bipolar disorder);

Joseph et al. [12] systematized the knowledge about the phenomenon of drug-induced mania and suggested the etiological division presenting 7 hypotheses grouped into 3 main blocks:

I. Iatrogenic effect:
   1. Ignition hypothesis;
   2. Scar hypothesis;
   3. Side effect hypothesis.

II. Incorrect evaluation of the natural course of BD:
   1. Vigilance hypothesis;
   2. Medication as irrelevant hypothesis.

III. Diagnostic error:
   1. False alarms hypothesis;
   2. Bipolar depression hypothesis.

For each of the theoretical models the authors determined:

- The potential contribution of the clinician in the induction of a manic episode. In some models, potential errors in thinking that lead to the diagnosis of a manic episode are taken into account;
- The level of "provocativeness" of the model, i.e., the degree of popularity, controversy and the media attractiveness. Contrary to appearances, it is not equal to the probability of a particular hypothesis on the basis of scientific evidence. Perhaps we should rather say that the controversial nature of a given hypothesis results from the level of the assumed 'harm' to the patient due to medical interventions. The most controversial models are those in which most (and in particular irreversible) iatrogenic effects burdening the patient are assumed or a diagnosis of drug induced-mania is questioned as inadequate in relation to the patient's symptoms;

– Potential probability based on the available scientific evidence subjectively assessed by the authors.

1. Ignition hypothesis

This hypothesis is the effect of pharmacotherapy as a 'triggering factor' for the induction of a manic episode in patients with biological sensitivity resulting from genetic susceptibility to induction of affective disorders. This hypothesis explains at least a 40-fold increase in the recognition of bipolar disorder in the United States as a result of an increase in the use of antidepressants in the population.

The potential role of diagnostician: destabilization of the patient after treatment with antidepressants, the use of which was somehow justified by the nature of the patient's symptoms.

The hypothesis is highly attractive, it is widely discussed but has no obvious scientific evidence to support its equity. The results of pharmacogenetic studies showing the relationship between genetic information and the side effects of pharmacotherapy could confirm this hypothesis

2. Scar hypothesis

The hypothesis assumes the influence of pharmacotherapy on the induction of permanent, harmful changes in the central nervous system in patients without biological burden.

The potential contribution of diagnostician: pharmacological sensitization of the patient for bipolar disorder.

The hypothesis is considered to be the most controversial and debatable because of the biggest impact of pharmacotherapy for the future functioning of the patient (it results in "permanent and adverse changes in a previously healthy brain" [12, p. 4]).

So far, we have found no studies confirming its probability, but there are several arguments against the above hypothesis. The ability to induce chronic and permanent changes in the central nervous system after a short, one-time exposure to a drug seems to be unlikely in the light of current knowledge on regenerative changes, adaptation and plasticity of the brain.

3. Side effect hypothesis

This hypothesis treats a drug-induced manic episode as one of the side effects associated with drug therapy, not as a 'real mood episode'.

Potential diagnostic error: diagnosis of affective episode instead of a problem from the group of side effects.

This hypothesis is consistent with the diagnostic criteria included in DSM IV TR, wherein "substance-induced mania" is placed among diagnoses related to medication side effect, not in the group of affective disorders.

The hypothesis does not seem attractive for media because of the little risk for the patient. The harmfulness of pharmacotherapy is understood as short-term effect, limited in time, which does not leave particularly negative consequences for the patient. The probability of the hypothesis remains difficult to determine. In order to confirm it, further studies indicating differences in the pathophysiology and course of bipolar disorder compared with pharmacologically-induced manic episodes would be required

4. Vigilance hypothesis

The problem of overdiagnosing drug-induced mania is explained as the result of excessive sensitivity, clinicians' 'vigilance' to discern the characteristic symptoms of a manic episode, increased control and especially careful monitoring of mood symptoms in studies.

The potential diagnostic error: overestimating the frequency of episodes of drug-induced mania, research bias.

The authors emphasize the attractiveness of affective disorders in children and adolescents for the media, which is associated with aspirations to publish a report of every diagnosed case of drug-induced mania.

This hypothesis is assessed as rather poor because the criticism is undoubtedly directed against the authors of the study. At the same time this hypothesis seems likely to be possible. In studies in larger groups of patients, the incidence of drug-induced mania is much lower than it would result from case studies.

5. Medication as irrelevant hypothesis

The hypothesis defines the drug-induced manic episode as an inadequate diagnosis, resulting from the incorrect interpretation of the natural course of bipolar disorder.

The potential diagnostic error: linking the patient's symptoms with the use of pharmacotherapy.

The level of attractiveness of the hypothesis is evaluated as low, mainly due to the minimal harm to the patient. The hypothesis is somehow removing the responsibility of the clinician for iatrogenic induction of an affective episode. The authors estimate a high probability of the hypothesis, however they highlight the lack of objective evidence and the need for further research.

6. False alarms hypothesis

This hypothesis, similarly to the previous one, assumes a diagnostic error which, in this case, consists in making an incorrect interpretation of symptoms of other disorders as manic episode. This error, among others, may be due to the difficulty in differentiating drug-induced manic episode with other behavioral effects associated with antidepressant treatment. It can also be an incorrect interpretation of changes in functioning of the patient after successful antidepressant treatment. The probability of this hypothesis is rated low, as is the level of provocation.

7. Bipolar depression hypothesis

The diagnostic error that underlies this hypothesis is based on the incorrect classification of depressive symptoms into a group of symptoms of unipolar affective disorder and consequently classification of manic symptoms as pharmacologically-induced mania.

The potential diagnostic error is the same as in hypothesis 5.

The media attractiveness of this hypothesis is assessed as high. The probability is also rated as high, which is confirmed by the data on a similar clinical manifestation of the first affective episode in both major mood disorders.

Recapitulation

Studies in adult patients with bipolar disorder confirm the negative effect of antidepressants on the induction of manic episodes. In the group of children and adolescents, the phenomenon of pharmacologically-induced mania is poorly understood and has been described relatively recently due to problems and controversies associated with the diagnosis of early-onset bipolar disorder. However, However, we should remember about the proven efficacy of antidepressants also in the special group of children and adolescents that is much higher than the possible risk of inducing a manic episode.

The fact that the drug-induced mania does not occur in all groups of patients treated with antidepressants undermines the assumption that it is only a side effect. It rather appears that patients who have shown symptoms of drug-induced mania are a group particularly vulnerable to the occurrence of bipolar disorder. Therefore a very important area for further research appears in prospective evaluation of young patients with a history of drug-induced manic episode. Potentially, these studies would answer the question of whether drug-induced manic symptoms are only the consequence of treatment or risk factors for bipolar disorder, or perhaps both.

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