Ziprasidone-induced hypomania

Dear Editor,

The literature mentions innumerable substances which may induce symptoms of mania and hypomania. Besides antidepressants, which are well described, we should highlight atypical antipsychotics, as they have been used as adjuvants in the treatment of affective disorders.[1-3] Cases of mania and hypomania induced by risperidone and olanzapine have been observed[1]; however, few and isolated reports are found for ziprasidone.[4,5]

A female patient, aged 79 years, had showed a state of discouragement, apathy, irritability and anxiety for five years. She arrived at our service using 60 mg/day of tranylcipromine with partial response. She reported non-treated previous depressive episode, when she was forty years old. She denied having had other physical diseases and was not taking other medications. In admission exams it was diagnosed hypothyroidism and introduced 75μg of levotiroxine. During ambulatory follow-up and after appropriate reposition of thyroid hormones, there was no remission of the symptoms. Thus, we chose to associate 40 mg/day ziprasidone at night. The depressive symptoms remitted in five days and evolved with acceleration of thought, increase of speech and pressure of speech, and mild day somnolence. It was raised the hypothesis of ziprasidone-induced hipomania and the medication was withdrawn, with improvement in the condition in less than one week. The patient was maintained with tranylcipromine and the depressive symptoms have not returned.

Mood cycling occurred in close temporal relationship with ziprasidone as soon as it was introduced and remitted after the withdrawal. No other medication was added in that same period. Possible organic causes, such as hypertireoidism caused by excessive hormonal reposition, were ruled out, as there were no significant alterations in routine laboratory tests and recent thyroid function.

Of depressed patients, a minority is resistant or intolerant to antidepressants, what makes necessary the use of other resources in the attempt of achieving better responses. The use of atypical antipsychotics has been disseminated as adjuvant in the treatment of mood pictures, both for manic episodes and for depression.[1-3] Ziprasidone is an atypical antipsychotic which has a great antagonist action in the dopamine D2 and serotonin 5-HT2a receptors, having also action on D3, 5-HT2c and 5-HT1d.[2,3] It has an agonist effect in 5-HT1a, besides inhibiting the neuronal reuptake of norepinephrine and serotonin.[2,3] The inducement of manic and hypomanic episodes with atypical antipsychotics is still not well explained; however, it has been proposed that the great affinity for the 5-HT2a receptor, particularly the 5-HT2a/D2 occupation ratio, be responsible for the mood alteration caused by these medications.[1,5] As ziprasidone has a high 5-HT2a/D2[2,5] occupation ratio, increased chances of causing mood cycling is suggested. Controlled clinical trials and naturalistic studies should be performed for a better understanding of these actions, preventing undesirable effects and allowing the widening of the indications of these medications.

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Epilepsy in the shadows of Brazilian psychiatry

Dear Editor,

For centuries, people with epilepsy have been stigmatized and kept far-away from society. Due to that, epilepsy has persisted as one of the most neglected medical conditions, mainly due to ignorance and superstition. In 1997 the World Health Organization (WHO), in association with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have launched a global campaign to 'bring epilepsy out of the shadows'.[1] The campaign's main goals are to increase the public and professional awareness about epilepsy as a treatable condition and to improve its public acceptability.

Epilepsy is the most frequent serious neurological disorder. It is estimated that there are up to fifty million people with epilepsy around the world, with 40 million living in developing countries. Point prevalence rates of active epilepsy

in the general population range from 0.4% to 1% and prevalence rates vary between 1.5% and 5%.[2] We estimate that in Brazil there are currently 1,800,000 people with active epilepsy and that 8,900,000 people have already had epileptic seizures at least once in lifetime. Epidemiological studies show a 28.6 to 58.3% prevalence of mental disorders for children with epilepsy[3] and 19 to 52% in adults.[4,5] We estimate that there are about 530,000 to 890,000 people with epilepsy and some associated mental disorder in Brazil.

It is within this context that we would expect a higher representation of epilepsy in the country's scientific events. The most recent example was the last Brazilian Congress of Psychiatry, performed in Goiania, in which, 10 lectures, three meetings with experts, 10 symposia, six presentations of clinical cases, 22 courses, 64 round-tables, three workshops, 13 industry symposia and 619 posters were presented. Out of these, only two clinical cases and six posters were related to epilepsy and associated mental disorders.

The stigma of mental disorders associated with epilepsy is probably due to the lack of skill and knowledge. In a survey performed with 157 psychiatrists in the congress (not-yet-published data), we observed that 53% of the interviewed considered that they had not received a formal education regarding mental disorders associated with epilepsy, 79% of them considered that their knowledge was insufficient for the treatment of those patients and 48% considered that psychiatrists have prejudice regarding epilepsy. The main claimed causes for this prejudice were difficulties in the treatment and lack of knowledge.

The stigma of psychiatrists can be hidden in the medical terminology, such as: the concept of 'behaviopathic' epilepsy, an erroneous diagnosis which is still applied in our society to certain violent patients who do not show even sufficient clinical evidence for the diagnosis of epilepsy or even the idea of 'epileptic crime', a violent act which by its specific characteristics would allow per se a diagnosis of epilepsy.[6]

This situation should be changed quickly.

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Study of prevalence of depressive symptoms and study of suicide risk in students of Ribeirão Preto, Brazil, assessed by the CDI

Dear Editor,

The Children's Depressive Inventory[1](CDI) is a self-reported questionnaire which measures the depressive symptomatology in childhood and adolescence. The goals of this study were to estimate the prevalence of the depressive symptomatology and the rate of suicide risk among students in the city of Ribeirão Preto. We used the CDI adapted and standardized by Gouveia,[2] adopting the cut-off point of 17. Of 3,280 questionnaires applied, only those in the age range between 7 and 14 years and whose people in charge gave their informed consent were incorporated in the study. Due to that the sample was reduced to 2,867 students. Estimated prevalence of the depressive symptomatology was 6.1%.

We studied the dependence on age and gender, according to the total punctual variation of the CDI. Mean punctuation of cases was 6.46 (SD=5.58). Mean punctuation among females was 6.63 (SD=5.70) and among males it was 6.27 (SD=5.46). The variation is not statistically significant (p=0.0818, according to Mann-Whitney test).

The table shows the CDI mean punctuation for the mentioned age range. In these eight age ranges the variation with age is statistically significant (p<0.0001 using the Kruskal-Wallis test). These results differ from the existent literature which shows higher rates of depressive symptomatology among adolescents.[3]

Table - Prevalence of depressive symptomatology of subjects aged 7 to 14 years.

Age	CDI punctuation
7	7.45
8	6.62
9	6.65
10	7.13
11	5.82
12	5.76
13	5.83
14	6.43
All	6.46

Regarding the question 9 of the CDI there are three possible answers: zero, absence of suicide ideation, one, presence of suicide intention, and two, suicide intention. Of the 175 subjects who reached the cut-off score, 24% answered item 2; 52% answered item 1 and 24% answered item zero, achieving, thus, 2.67% of cases with suicide risk. In the population who did not reach the cut-off score, 1.25% (35 cases) answered item 2; 22.40% answered item 1 and 76.35% answered item zero. These results show that suicide risk can occur also among subjects who have not depressive symptoms according to the CDI.

According to the literature, the depressive disorder is very common, affecting 3 to 8% of children and adolescents.[4] The

results of this study reinforce the importance of not considering the depressive symptomatology as a transient process, and attention should be given to the symptoms shown in different age ranges. The psychiatric assessment should intervene in the symptomatology screened in the population for the diagnosis and treatment, therefore, acting the earliest possible in the secondary prevention, preventing thus the possible health and economical burden for the individual and society.

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Acute delusional episodes prevented by ketoconazole

Dear Editor,

The ICD-10 diagnostic category of acute and transient psychotic disorders seems to be related to different etiological factors[1]: 'reactive' and 'organic psychosis', acute mixed affective states, acute psychotic presentation of: a) an 'up-to-that-point' latent 'simple' form of schizophrenia; b) paranoid personality disorder; c) emotionally unstable personality disorder. However, a more detailed semiological-nosographical dissection seems capable of individualizing a "purer" presentation of this disorder, which is linked by some authors to a depressive/anxious diathesis.

These patients often display anguished/perplexed/terrorized delusions with fear of the End of the World, eschatology, dramatic wars, imminent peril to themselves and their relatives, terrible diseases, fires and mortal persecution (the so-called 'apophany', wrongfully described by Conrad in his 'Die Beginnende Schizophrenie' as a diacritical symptom of schizophrenia).[1]

Stressors, even when moderate, seem to play a role in precipitating such psychotic episodes.

These patients seem to have a kind of predisposition to develop full and more classical depressive episodes in the future[2]. On the other hand, it is well known that hypercortisolism and other hypothalamic-pituitary-adrenal (HPA)anomalies are quite common biological findings in depression and other manifestations of affective diseases.[3]

We therefore began to test the hypothesis, which has already been done by others,[4] that such psychotic episodes could be mitigated or hindered by a pharmacological strategy such as blocking such HPA reported hyper-reactivity with ketoconazole (50-100 mg once a day). Four women, ranging from 20 to 42 years of age, have been presenting acute anguished/perplex/terrified delusional episodes one or two times a year even when under supposedly effective psychopharmacological treatment (antidepressants, antipsychotics and mood stabilizers). Such treatments were not able to conveniently and entirely hinder those psychotic episodes in each occurrence.

Patient one: 20 years old, under lithium (1,200 mg/d), clomipramine (200 mg/d) and clozapine (200 mg/d). After the beginning of the experimental treatment, four years ago, was taking ketoconazole 100 mg/day and lorazepam 2 mg/at night 'ad libitum'.

Patient two: 28 years old, under sodium valproate (1,500 mg/day), fluoxetine (60 mg/day) and quetiapine (150 mg/d). After the experimental treatment: ketoconazole 100 mg/d and fluoxetine - 20 mg/d.

Patient three: 36 years old, under lamotrigine (200 mg/d), olanzapine (15 mg/day). After treatment: only 50 mg/day of ketoconazole.

Patient four: 42 years old, under topiramate (150 mg day) venlafaxine 150 mg/day, and risperidone 4 mg/day. After treatment : ketoconazole'100 mg /day and venlafaxine 37.5 mg/d.

Transitory fatigue was the only reported side-effect of ketoconazole in this sample.

After we began prescribing ketoconazole to these patients, four years ago, only one patient relapsed in a single occasion, which seems to support our initial hypothesis.Obviously, controlled and well-designed experimental trials are needed to confirm or refute such findings.

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Commentary about the editorial "Who pays the impact?"

Dear Editor,

Regarding the editorial page 'Who pays the impact' Considerations on conflict of interest ("Quem paga o impacto? Considerações sobre conflito de interesses"; Rev Bras Psiquiatria 2003;25(3):129-30), we consider quite appropriate at this moment the discussion proposed by the author, as in our country there are few official resources for research and the pharmaceutical industries end having more space than expected for them.

Reflecting on the data presented by the author we can infer that one of the biases could be overcome using together the quantitative and qualitative methods. A good example would be research on the improvement of the quality of life of people with specific pathologies after using a specific medication. Most of this kind of research uses the quantitative methodology, when the joint utilization of both methods would produce a deeper understanding of the issue. In this case, the fact that qualitative methods stimulate a deeper knowledge of the phenomenon would allow to know at each point, actually, the quality of life of the individual has improved and where it has worsened due to possible side-effects, an understanding which is extremely important to predict, for example, compliance with treatment.

According to Greenhalgh[1] one of the reasons for the scarce utilization of the qualitative methodology in the medical area would be the little knowledge of researchers about this methodology. This lack of knowledge is partially due to the nomothetic characteristics[2] of the quantitative method, in which a great generalization is achieved, although at the cost of a little understanding of the phenomenon. This characteristic agrees more with the sponsoring offered by the pharmaceutical industry. Against the argument that qualitative research does not produce reliable information, the same author warns that any badly formulated and managed research – be it quantitative or qualitative – generates doubtful results and provide they are adequately applied to the correct phenomenon, qualitative methods have as much validity as quantitative methods.

Other negative consequence of this scarce knowledge, according to an article of Pope and Britten (1993) cited by Greenhalgh, is that good articles with qualitative methods are sometimes rejected due to the scarce familiarity of reviewers with this type of article, whereas from time to time bad articles are published, leading to the conclusion that some reviewers seem sometimes unable to distinguish good from bad qualitative research.

We are not here setting aside the good points of quantitative research, but were are only highlighting that higher knowledge and utilization of the qualitative methods would result in a deeper understanding of the results obtained by this type of research. Their use would provide to the medical area the necessary understanding of the environment of the relationships subject-medication, subject-treatment, etc, enabling a higher knowledge, control and prediction of the phenomena originated from this interaction. Lastly, the qualitative study also contributes to a more humanist view of this relationship.

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