Facial and bilateral leg edema in a patient using quetiapine

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Dear Editor,

Quetiapine is an atypical antipsychotic approved for the treatment of schizophrenia, bipolar disorder, and along with an antidepressant to treat major depressive disorder. It is also sometimes used off labelly as a sleep aid because of its sedating effect.

Quetiapine's mechanism of action is not fully clarified though involves antagonism at serotonin type 1 (5-hydroxytryptamine [5-HT_{1A}]) and type 2 (5-HT_{2A}, 5-HT_{2C}) receptors with relatively weak antagonism at dopamine (D_1, D_2) receptors[1]. Additionally, quetiapine exhibits some α_1-adrenergic antagonism that could explain its cardiovascular side effects, like orthostatic hypotension[2]. Bilateral leg edema has been infrequently described with several atypical antipsychotics, including case reports with olanzapine[3,4], risperidone[5], and ziprasidone[6]. Currently, there are some published cases of peripheral edema related to quetiapine in literature[7-12] and one case with facial, eyelid and added bilateral lower extremity edema[13]. Edema is not presently listed as a potential complication in its prescribing information. Here, we report a case exhibited both face and leg edema associated with quetiapine use.

Case report

A 54-year-old female patient with bipolar affective disorder was admitted to our outpatient psychiatry clinic for facial and bilateral leg edema. She had been hospitalised in a mental health hospital for a manic psychosis episode, treated with haloperidol and quetiapin for about one month. She was discharged on haloperidol decanoate 50 mg(miligram)/ml(mililiter) and quetiapine 600 mg/day. She developed 2+ bilateral leg and face edema after 8 days from hospital dismission. Cardiac and pulmonary exam and blood pressure measurements were within normal limits. Laboratory work-up was unremarkable thyroid stimulating hormone (TSH), albumin, electrolytes, blood urea nitrogen (BUN), creatinine, liver function tests (AST, ALT, GGT) erythrocyte sedimentation rate, N-terminal fragment brain-type natriuretic peptide, complete blood count with differential and urinalysis). In accordance with cardiology consultation, treatment with furosemide started which decreased edema 1+ bilaterally. We did not suspect haloperidol decanoate to be the cause of edema in highlight of the literature but there were some cases of quetiapine associated peripheral edema[7-13]. One week after decreasing the dose of quetiapine from 600 to 300 mg/day, edema had ameliorated. No other furosemide treatment were followed through. In spite of other reported cases, our case experienced edema after 38 days of quetiapine use and she suffered both face and leg edema simultaneously. In follow-up period one year later, when she was prescribed another labeled quetiapine from a different hospital, facial and leg edema recurred.

Discussion

Extensive cardiovascular and metabolic work-up further failed to reveal alternative explanations. Our case was using Haloperidol decanoate but no change in this medication implemented around the time of edema formation and resolution. The onsets and offsets of edema were temporally correlated to changes in dose of quetiapine. Edema followed consumption of quetiapine for one month and resolved shortly after dose decrement. Furosemide was briefly applied for symptomatic relief only.

The Naranjo algorithm, Naranjo scale, or Naranjo nomogram is a questionnaire designed for determining the likelihood of whether an ADR(Adverse Drug Reaction) is actually due to the drug rather than the result of other factors. Probability is assigned through a score termed definite, probable, possible, or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding ADRs. It is also called the Naranjo scale or Naranjo score. Score can range from 0 (doubtful ADR) to ≥9 (definite ADR), detailed scoring is described as follows:[14]

- ≥9= definite ADR
- 5–8= probable ADR
- 1–4= possible ADR
- 0= doubtful ADR.

Our patient had a score of 7, which means this is a probable ADR with quetiapine.

With only one case report, a dose-dependent relationship between quetiapine and leg edema can not be clearly established. In the case described by Rozzini et al. (2005) a dose increase from 100 mg to 150 mg quetiapine daily was followed next day by bilateral leg edema[12]. Correspondingly our report describes symptomatic improvement when the quetiapine dose decreased but not discontinued, perhaps suggesting a dose-response relationship. Time to appearance of leg edema after initiation of quetiapine was one month. Time to resolution after drug discontinuation was one week.

Quetiapine is an antagonist for several neurotransmitter receptors, including serotonin 5-HT_{1A} and 5-HT_2, dopamine D_1 and D_2, histamine H_1, and α_1- and α_2- adrenergic receptors[1]. Whilst potential mechanisms for antipsychotic-induced edema persist to be speculative, prior study has proposed a relationship between dopaminergic antagonism and idiopathic edema[15-17]. Through a variety of receptor subtypes, dopamine may effect natriuresis, epithelial fluid resorption, vascular smooth muscle relaxation, and the renin-angiotensin system[10,18-20]. Given that quetiapine is considered a comparatively weak dopaminergic antagonist[21], a different mechanism may seem more plausible. Notably, quetiapine exhibits 5-HT_2 antagonism. Some authors hypothesise 5-HT_2receptor blockade may account for olanzapine-induced leg edema through with increase in cyclic adenosine monophosphate levels that can ultimately lead to vascular smooth muscle relaxation[3,22]. Alternatively, α_1-adrenergic blocking activity of atypical antipsychotics considered to explain cardiovascular side effects like orthostatic hypotension, dizziness and reflex tachycardia[2,10,20]. Alpha-adrenergic-mediated peripheral vasodilation has also been proposed as a possible mechanism for olanzapine-induced edema[3,21]. Since quetiapine and olanzapine demonstrate similar affinity to the α_1-adrenergic receptor[2] and share similar propensities for orthostatic hypotension, an analogous mechanism for quetiapine-induced edema could be proposed.

An allergic reaction could pose an alternative explanation for drug-induced edema. This was reasoned to be the most likely explanation for ziprasidone-induced edema but in our case report where edema started after one month allergic reaction is less possible. Unfortunately our laboratory does not possess IgE, C3 and C4 level kits and this can be considered a limitation.

The mechanism of quetiapine-induced edema remains uncertain though likely parallels that of other second-generation antipsychotics. Further clinical observation and research is needed to clarify the characteristics, risk factors, dose-dependence, and potential mechanisms of quetiapine-associated edema[10,20]. We hope our report will alert physicians to this potential vascular complication to promote prompt recognition and intervention.

CONFLICTS OF INTEREST

None to declare.

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Gender violence and mental health: a gap between clinical assistance and research

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Dear Etitor,

The impact on Mental Health in women victims of gender violence is neither detected, nor studied and it constitutes a gap in Clinical Assitance in general practice in Mental Health Services and Clinical Research. In a recent review by Oram, Khalif and Howard published in Lancet, in November 2016, the problem of violence against women is reviewed as one of the most prominent problems in Mental Health. Mental Health professionals should identify, prevent and respond more effectively to what is being done so far. Violence against women and Mental Health are closely related. Having a mental disorder is a risk factor for suffering gender violence. The effects of gender-based violence on women's mental health are widely documented: depressive disorders, anxiety disorders, adaptative disorders, post-traumatic stress disorder, sleep disorders, as well as a higher prevalence of alcohol and substance use disorders, eating behavior disorders and alcoholism.

There is poor detection of clinical cases. It overlooks the greater vulnerability of diagnosed women with a serious mental disorder from suffering gender violence. The most common forms of violence against women are partner abuse and sexual violence. Although the WHO Clinical Guidelines address the role that Mental Health professionals should play in identifying violence against women, and responding appropriately, there is still a minor identification of cases with violence. This causes an inadequate follow-up in the corresponding services because it doesn't respond to their demands and, as a consequence, there is a poor response to treatment. It seems that gender-based violence and mental disorders were in separate fields for Public Health.

The lack of detection of cases of gender violence is not a reflection of the lack of equality in our society, where social inequity is also reflected in Mental Health, being gender violence the tip of the iceberg. Psychiatric pathology is detected through international classifications and, on many occasions, the victims of gender-based violence do not feel well assisted when the underlying nuclear problem is not given the appropriate attention, and it has delimited, to a greater or lesser extent, the subsequent clinical situation. It is not detected, and it is neither adequately attended. We have a care problem that affects both victims of gender violence and perpetrators, who are not given adequate psychiatric and/or psychological care.

The problem is not only assistance, but also the means and the available resources. There is little research on how to improve the identification and treatment of victims and perpetrators in contact with Mental Health. However, it seems clear that Psychiatric Services can play a relevant role in primary and secondary prevention in violence against women. We are facing a clinical challenge and a major ethical dilemma since gender violence appears disconnected from Mental Health, and it is not considered a specific assessment. It is necessary to treat this fact in order to make a better clinical approach to the symptoms that are presented. Although the clinical criteria for a particular psychiatric disorder (using the use classifications) are met, due to the the magnitude of the problem of gender-based violence in our society, it should be taken into account in the assessment of any woman in a systematic way. And adequate to problems such as chronic anxiety which, in many cases, it is a reflection of the violence suffered. The goal is to develop strategies for prevention and to improve the future prognosis of

many women treated in our devices. We can not continue to look elsewhere because we participate in denying the prevalence of gender violence and its consequences for women's mental health.