Clozapine-Induced Pericarditis: An Overlooked Adverse Effect

To the Editor:

Clozapine is an atypical antipsychotic with a wide range of adverse effects. It is important for clinicians to be aware of these side effects because many of these are life threatening. Even though myocarditis is a well-known serious cardiac adverse condition, pericarditis associated with clozapine use is also gaining attention (1-3). Here we report a case of clozapine-induced pericardial effusion and paracardiac pleural effusion.

Case Report: Ms. L, a 45-year-old woman, presented with a chronic schizophrenic illness characterized by delusion of persecution, reference and third person discussing type of auditory hallucinations of eleven years duration. She was on treatment with tablet chlorpromazine up to 400 mg for almost five years and risperidone 6 mg for the next one year. She had not improved with these two trials of antipsychotics. Ms. L had developed severe tardive dyskinesia (TD), which involved the oro-bucco-lingual region resulting in severe impairment in speech. The Abnormal Involuntary Movements Scale (AIMS) rating was 24. Her speech was almost incomprehensible, and she had to use gestures while communicating to others due to the TD. In view of the failure of two antipsychotics and due to the presence of debilitating TD, she was started on clozapine and the dose was escalated gradually up to 300 mg per day. It was ensured that the dose escalation was slow, starting from 12.5 mg per day as per *Maudsley Prescribing Guidelines* (4). The baseline and follow-up blood counts were normal, and the baseline ECG was within normal limits. On the third week after starting clozapine, she developed fever (102° F), cough, chest pain of constricting type and dyspnea. The blood picture was that of neutrophilic leucocytosis without eosinophilia. The liver function test, renal function test and electrolytes were within normal limits. She did not respond to an antibiotic course of tablet levofloxacin 500 mg twice daily for three days. Subsequently, an emergency medical opinion was sought. The chest x-ray revealed paracardiac pleural effusion and echocardiogram revealed the presence of pericarditis and pericardial effusion. Other causes of pericarditis were ruled out by the cardiologist who managed her conservatively with discontinuation of clozapine. The cardiac troponins were in normal range.

The symptoms resolved in four days and, by the tenth day, chest x-ray and echocardiogram were normal. The patient was subsequently started on tablet olanzapine up to 20 mg per day. There was 30% reduction in her symptoms with a six-week trial of olanzapine. She reported that the fearfulness and "voices" had come down to some extent and she was seen interacting better with others. However, on mental state examination, she still had the delusions which she had previously reported. She was also initiated on benzodiazepines (clonazepam 1 mg twice daily) for the treatment of TD, taking into consideration some preliminary evidence for this group of medications in TD (5).

Discussion: The cardiac side effects of clozapine are potentially life threatening. Pericarditis and related pericardial effusion have been noted in some of the previous reports (6, 7). This report—which adds to the previous literature—raises concern about the risk of acute cardiac side effects in patients treated with clozapine (3, 8). The Naranjo Adverse Drug Reaction Probability Scale suggested a probable relationship between clozapine use and this adverse event (9). As reported previously in some papers, the patient in this report was managed conservatively with stoppage of clozapine (1, 3, 6). Some of the patients in the previous reports on this adverse event had developed serious associated concerns like cardiac tamponade and required pericardiocentesis (2). There was no evidence for associated polyserositis in our case in contrast to some other earlier reports (10, 11). The blood picture in our patient was devoid of eosinophilia even though, previously, eosinophilia as an indicator of clozapine-induced pericarditis has been reported (12).

Even though pericarditis is unpredictable and relatively uncommon, it merits attention and early intervention when the pertinent clinical symptoms occur. It is important for clinicians to be aware of this adverse event.

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Pathological Bone Mineral Density in Patients on Long-Term Risperidone

To the Editor:

We have read with great interest the article entitled "Bone Loss Associated with Hyperprolactinemia in Patients with Schizophrenia" by Kinon et al. (1), which concerns the prevalence of low bone mineral density (BMD) in schizophrenic patients treated with conventional antipsychotics or risperidone. The article reports that hyperprolactinemia during treatment with antipsychotic drugs may be associated with a higher rate of low bone mass in men compared to women. We would like to contribute to this controversial discussion by comparing the results obtained by Kinon et al. with our own findings regarding the evolution of BMD in both men and women (2). In fact, we believe that our investigation nicely complements the data obtained by Kinon et al., permitting us to draw a more thorough conclusion with regard to this interesting topic.

Our data concerning BMD were obtained using a logistic regression model to predict the risk of developing osteopenia and osteoporosis based on estradiol levels and duration of parenteral risperidone treatment. We studied a cohort of outpatients (n=58; all Caucasian; 63% female; 44±16 years old) that was diagnosed with schizophrenia (68%) or schizoaffective disorder (32%) and were recruited from the Nuestra Señora de Gracia Hospital (Zaragoza, Spain). All patients had been treated with long-term parenteral risperidone (52±24 mg for 6±3 years), allowing us to identify the time at which pathological BMD emerged.

Analyzing the odds ratios (OR) associated with pathological BMD in both men (n=21) and women (n=37) separately, we observed that the risk of this complication increased year by year. Notably, the highest risk of osteopenia (T-score <-1 and >-2.5) occurred within the fourth year of treatment for both females (n=37; OR=5.3; 95% CI=1.9144–14.7658; p=0.0013) and males (n=21; OR=2.4; 95% CI=0.5114–11.2632; p=0.2671). In contrast, we observed the highest risk of osteoporosis (T-score ≤2.5) within the seventh year of treatment in women (n=37; OR=3.2; 95% CI=1.4141–9.3145; p=0.0270) and the seventeenth year in men (n=21; OR=4.5; 95% CI=1.0071–20.1067; p=0.0489).

Furthermore, our investigation revealed that hypoestrogenism (estradiol <40 pg/mL) was present in 75% of females, whereas hypogonadism (testosterone <3.0 ng/mL) occurred in 42% of males. This data suggest that hypoestrogenism and hypogonadism, which are secondary to the administration of risperidone, may contribute to risk for pathological BMD over time.

Indeed, our study had limitations, which include small sample size and the fact that no other BMD determinants were evaluated (e.g., heredity, dietary factors, alcohol, tobacco, coadjuvant drugs, endocrine factors [excluding estradiol], mechanical forces, and risk factor exposure). However, by following our patient cohort over an extended period of time and applying a logistic regression model based on estradiol levels (established as a critical steroid regulating bone metabolism in men and women) (3) and duration of antipsychotic treatment, we were able to quantify the risk of developing osteopenia and osteoporosis.

Therefore, we believe that our findings are complementary to the data recently reported by Kinon et al. Taken together, these investigations highlight that men have a higher risk of developing risperidone-induced osteoporosis (low BMD) than women. Nevertheless, the occurrence of this complication appears later in men than in women (17 *vs*. 7 years, respectively), which likely results from the effect of low testosterone on bone resorption in men (as stated by Kinon et al.).

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Sustained Improvement of Negative Symptoms in Schizophrenia with Add-On tDCS: A Case Report

To the Editor:

Negative symptoms in schizophrenia have been demonstrated to be associated with significant disability even after the improvement of positive psychotic symptoms (1). The relative refractory nature of negative symptoms—in comparison to the positive symptoms—has made this domain of illness a considerable treatment challenge (2, 3). Negative symptoms are considered to be due to hypofunctional dorsolateral prefrontal cortex (DLPFC) (4). Novel brain stimulation strategies such as transcranial direct current stimulation (tDCS) have an advantage of selectively stimulating and inhibiting different brain regions, thus enabling us to target specific symptom dimensions of schizophrenia (5). In this report, we describe a patient with schizophrenia who demonstrated significant and sustained improvement in negative symptoms with a marked functional improvement after use of tDCS administered with anodal stimulation of left DLPFC.

A 22-year-old right-handed woman, who was previously pursuing graduate course in computer sciences, presented with three-year duration of *DSM-IV* schizophrenia. She reported auditory verbal hallucinations characterized by commenting voices with derogatory content. She did not have any other positive symptoms. In addition to this, her relatives reported that she lacked initiative and motivation in addition to being disinterested in many of her previously pleasurable activities such as meeting friends and reading books. She also reported difficulty in concentrating and, hence, had dropped out of her classes. She had been treated with risperidone in a dose of 4 mg in the past with inadequate response. Subsequently, she had shown initial response to the typical antipsychotic, trifluperazine, which was initiated by a local practitioner. However, the benefit obtained with trifluperazine dwindled gradually and she was then referred to our center. She was also on 1 mg of trihexyphenidyl since there was history suggestive of slow movements and tremors (extrapyramidal symptoms) after initiating trifluperazine. She was already on this regimen when she was referred to us, and we decided to try tDCS as the next treatment option after discussing the available treatment options with the patient and her family members. During the initial visit, the severity of auditory hallucinations—as measured using the Auditory Hallucinations Rating Scale (AHRS) (6)—was 24. Her negative syndrome score as assessed by SANS was 18 (7). She continued to have amotivation and lack of interest despite being on medications. Neurological examination did not reveal evidence of extrapyramidal symptoms and mental status examination was not suggestive of any symptoms of depression. She did not have history or clinical features suggestive of neurological/medical disorder, developmental delay or mental retardation. In view of persistent auditory hallucinations, she was started on tDCS without any alterations to her ongoing medication dosage. Written informed consent was obtained from the patient after explaining the procedure in detail.

tDCS was given using a standard equipment (Neuroconn DC Stimulator Plus, http://www.neuroconn.de/dc-stimulator_plus_en/)—as per previous description (8)—with stringent safety measures (9). The anode was placed with the middle of the electrode over a point midway between F3 and FP1 (left dorsolateral prefrontal cortex) and the cathode was located over a point midway between T3 and P3 (left temporo-parietal junction) (8). The stimulation level was set at 2 mA for twenty minutes. During the tDCS sessions, the patient was comfortably seated and did not perform any activity. The sessions were conducted twice a day (separated by at least three hours) for five consecutive days (8). The patient tolerated tDCS well, without any adverse effect as ascertained by a structured questionnaire after each session (9). Baseline SANS score was obtained one hour prior to the first tDCS session. The improvement was measured by periodically interviewing the patient as well as the family members.

Immediately after the tDCS (after five days), there was no change in SANS score. Interestingly, in the subsequent two weeks after tDCS, she showed a remarkably rapid improvement in motivation level, speech output, affective response and interpersonal interactions (SANS score=12); this was appreciated by her family members as well. Moreover, she also reported that she could concentrate better and started going to her classes regularly and was able to socialize well with her friends and peers. The medications—as earlier described—were continued during this intervening period. During follow-up reassessment at six months, she demonstrated persistent improvement in negative symptoms (SANS score of 7), with minimal change in auditory hallucinations (AHRS score of 15). The patient continued to report auditory hallucinatory experiences, which were distressing even though there was some improvement. She could only perceive a mild reduction in the intensity and "loudness" of voices, which disturbed her. She also reported that the space/location from which voices were perceived moved farther away. These changes were not satisfactory for her and she would continue to mention the "voices" to her family members.

Improvement in hallucinations with tDCS has been reported previously (8, 10). To the best of our knowledge, this is one of the initial reports of sustained improvement in negative syndrome with tDCS in a patient with schizophrenia. Another related report that we are aware of is the case description of transcranial Random Noise Stimulation improving negative syndrome (11). However, in that

report, the duration of sustained benefit was not specified. In a recent report with a study observation period of two weeks, tDCS was found to result in improvement in negative symptoms by about 25% in a patient (12). However, in our patient we observed that improvement occurred gradually and had significant change at the end of six months, demonstrating a sustained benefit without requirement for further tDCS sessions in the follow-up period.

In our patient, there were no depressive symptoms; no medication alteration was done during the six-month period. Moreover, the negative symptoms showed a rapid and sustained improvement despite minimal change in positive symptoms. All of this supports that the improvement is highly likely to be due to the effect of tDCS rather than to be mediated by factors that contribute to "secondary" negative syndrome.

The ability of tDCS to improve negative symptoms might be due to correction of prefrontal hypometabolism/hypoperfusion or due to selective activation of the mesocortical dopamine system (13). In addition, tDCS has been reported to modulate gamma-aminobutyric acid (GABA) signalling, thereby demonstrating the differential effects based on anodal or cathodal stimulation (14). Increased perfusion in brain areas connected to the DLPFC and decreased functional coupling between the left DLPFC and the thalami bilaterally after facilitatory anodal tDCS on DLPFC has been reported recently (13). Moreover, tDCS has been shown to result in sustained adaptive effects on cognitive function over a period of six months (15). It is possible that these mechanistic effects might have mediated improvement of negative syndrome in this patient. Another non-invasive brain stimulation technique—repetitive transcranial magnetic stimulation (rTMS)—has been found to be useful in treating auditory hallucinations. However, the evidence for effects of rTMS in treating negative symptoms has been equivocal (16). Hence, the clinical utility of add-on tDCS for the treatment of negative syndrome needs further systematic exploration.

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