Antidepressants and its relationship with microscopic colitis

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Dear Editor,

Serotonin reuptake inhibitors (SSRIs) are the antidepressants more widely used in psychiatry and they are frequently associated with gastrointestinal side effects when started[1]. Sertraline seems to have the greatest incidence of diarrhea as side effect among the SSRIs[2]. However, this symptom may mask a microscopic colitis, an illness that has been associated with the use of antidepressants and, specially, with the use of SSRIs. This gastrointestinal illness requires a more thorough medical evaluation because it usually needs specific therapeutic management to improve patients´ quality of life[3].

Case report

A 55-years-old woman was evaluated in the Psychiatry department because of low mood. Regarding her medical history, she had a pacemaker due to supraventricular fibrillation and she had valvular prostheses due to mitral and tricuspid rheumatism stenosis. Regarding substance use, she admitted sporadic use of alcohol currently and smoking cessation 30 years ago. She denied consumption of other substances. As a psychiatric history, she had been suffering from anxiety-depressive disorder for 10 years, for which she had previously received antidepressant treatment (trazodone and fluoxetine) and benzodiazepines, without significant side effects, as well as complementary psychotherapeutic treatment. She denied psychiatric family history. Because of new affective worsening, pharmacological treatment with sertraline was started at a dose of 50 mg/day.

Twenty days later, the patient was assessed in Gastroenterology department due to an increase in the number of liquid stools (up to 12 stools/day) and consequent weight loss. Complementary tests were performed (colonoscopy and biochemical, blood count and coagulation analysis) but no alterations were observed. However, in the colon biopsies taken during the colonoscopy were observed pathological increase of intraepithelial lymphocytes and increase of the lymphoplasmacytic infiltrate in lamina propria.

The diagnosis was microscopic colitis because of sudden onset of the clinical symptoms, temporal correlation with the sertraline treatment and the histopathological findings. Antidepressant treatment was stopped and oral budesonide 9mg/day was started. Progressively, there was an improvement in the clinical picture consisting in the reduction of daily stools numbers and weight recovery. After completed 4 weeks of treatment, the dose of budesonide was progressively decreased without evidence of diarrhea recurrence. Regarding antidepressant treatment, after cessation of corticosteroids, vortioxetine 10 mg/day was initiated with adequate mood evolution and without the onset of microscopic colitis symptomatology. No further tests were carried out by Gastroenterology department due to good evolution.

Discussion

The use of SSRIs in anxiety-depressive disorders is widespread in clinical practice. Some of the most frequently reported side effects associated with the use of SSRIs include gastrointestinal effects (nausea, diarrhea, dyspepsia and abdominal pain). Approximately half of all patients started on these agents experience gastrointestinal side effects mainly in the first few days following treatment initiation[1]. Specifically, a meta-analysis from 2011 found that sertraline has the highest incidence of diarrhea when is compared to other SSRIs and venlafaxine[2]. The mechanisms underlying the association between serotonin antidepressants and diarrhea are unknown. However, this group of antidepressants play an important role in the gastrointestinal tract motility through the release of serotonin at the intestinal level by stimulating enterochromaffin cells[1,4].

The differential diagnosis in a case of diarrhea after the start of antidepressants must include microscopic colitis. It clinically presents with chronic diarrhea and is characterized by normal colonic mucosa at the macroscopic level and a distinctive histological inflammation at the microscopic level. It classifies into collagenous colitis and lymphocytic colitis according to the histopathological findings. Its annual incidence is estimated between 2-6 cases/100,000 inhabitants, without ethnic differences and affecting predominantly women (ratio 7:1) with an average age of 60-70 years[3,5].

Its etiology is unknown and, probably, multifactorial. Genetic, immunological and infectious factors have been associated, as well as the use of tobacco. Drugs have been suggested as causal factors, including antidepressants and, specially, SSRIs. The mechanism through which drugs can cause this disorder is unknown. The likelihood of association derives from the temporal relationship between the start of treatment and the development of symptoms, as well as the disappearance of symptoms with the withdrawal of the drug. The diagnosis is based in the characteristic histopathological findings of colon biopsies as well as the screening of other pathologies. Regarding treatment, if the symptoms persist

Table 1 Case reports of microscopic colitis associated to antidepressant use

Reference	Gender	Age	Symptoms	Causal drug	Treatment
Gwillim y Bowyer[9]	Woman	50 years	Watery diarrhea	Duloxetine	Duloxetine interruption
Menon y Ng[10]	Man	63 years	Watery diarrhea	Sertraline	Sertraline interruption
Marques et al.[11]	Woman	41 years	Watery diarrhea	Sertraline	Sertraline interruption
Bahin et al.[12]	Woman	75 years	Watery diarrhea	Duloxetine	Sertraline interruption
Sisman et al.[13]	Woman	66 years	Watery diarrhea	Duloxetine	Duloxetine interruption + budesonide 9 mg/day
Kusnik y Stolte[14]	Woman	80 years	Watery diarrhea	Duloxetine	Duloxetine interruption
Béchade et al.[15]	Woman	65 years	Watery diarrhea	Mianserin	Mianserin interruption + budesonide 9 mg/day

despite the withdrawal of the possible causative drug, oral budesonide is the only effective therapy in quality studies[3,5].

Several studies, mostly in the form of case reports, have pointed out the possible association of antidepressant drugs with microscopic colitis, especially SSRIs although not exclusively that pharmacological group (Table 1). One of the first research articles to associate the use of SSRIs with microscopic colitis dates from 2004[6]. This study, with a sample of 199 patients, found a possible chronological relationship of microscopic colitis with the introduction of paroxetine (one identified case) and with the introduction of sertraline (seven identified cases). Subsequently in 2005, sertraline and paroxetine were found to have a high and intermediate risk level, respectively, in a scoring system to identify and determine the odds that a drug could cause microscopic colitis[7]. Equally, a prospective case-control study found that SSRIs consumption was associated with an OR=21 (2.5–177.0) of producing collagenous colitis and with an OR=37.7 (4.7–304.0) to produce lymphocytic colitis[8]. A subsequent study carried out by the same team of researchers confirmed the use of SSRIs as a risk factor for the development of microscopic colitis (p=0.029), being sertraline treatment as an independent risk factor in the multivariate analysis with an OR=17.5 (2.0–149.2)[4].

In conclusion, despite the high incidence of gastrointestinal adverse effects associated with the use of antidepressant drugs, these symptoms should not be underestimated because the potential risk of being in front of greater severity illness such as microscopic colitis. According to the previous literature, the risk is higher when the antidepressant treatment is with SSRIs and, specially, with sertraline. Therefore, in the presence of chronic diarrhea in patients with antidepressant treatment, it is recommended to assess their referral to Gastroenterology department for the implementation of complementary tests, such as colon biopsy, which can rule out this illness.

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Effectiveness of a non-sedative intervention to prevent anxious and claustrophobic reactions in magnetic resonance imaging

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Dear Editor,

MRI experience is often described by patients as strange and uncomfortable[1]. In clinical series, a considerable number of resonances must be interrupted due to the appearance of panic attacks. Some authors place around 2% the frequency of anxiety reactions that occur during the MRI. The number of MRIs that finally have to be aborted may be close to 1%[2,3]. All this might lead to a delay in the diagnostic procedures, as well as to delays in waiting lists and economic losses for the Health System.

Many of the published works consider the diagnosis of claustrophobia in the solely presence of anxiety symptoms, without performing a psychopathological assessment of any kind in those patients[2]. However, claustrophobia, which is defined as a fear of closed spaces, tends to persist over time and to appear, in the same patient, in closed spaces of different nature[4].

Several authors have proposed the use of deep sedation protocols to prevent anxiety reactions[5]. However sedation, even when relatively mild, can involve several risks, such as the appearance of hypoxia[6], which results in the need for extensive monitoring. The works that specifically describe pre-medication protocols through the use of benzodiazepines are scarce[7-9]. The use of "open" MRI devices, apparently less anxiogenic, may be another choice in cases in which classical MRI has not been possible[2]. Nevertheless, the availability of these devices in the Spanish Health System is still low, and their magnetic field strength is significantly lower[10].

In the present work, we describe a brief pre-medication protocol with alprazolam, as an alternative to open MRI. In addition, the effectiveness of the intervention is evaluated and diagnostic factors associated with its success are considered.

Methods

Study setting

At the end of 2012, the Medical Direction of the Henares Hospital (Coslada, Madrid, Spain) asked the Department of Psychiatry for a diagnostic and therapeutic intervention on the patients who were on the waiting list for open MRI. The purpose was to redirect some of these patients to conventional MRI and thus alleviate the waiting list. The present work is a retrospective observational study of that intervention.

Patients

From January 2013 to December 2015, all patients who met the following criteria were consecutively included: 1) Age over 18 years; 2) Having given their informed consent; 3) Being on the waiting list for open MRI either by direct indication of the prescribing physician based on suspected claustrophobia or by interruption of a closed MRI for anxiety symptoms. Only patients requiring urgent MRI were excluded from the study.

Assessment and intervention

All included patients were interviewed, on one occasion, by an experienced psychiatrist. Sociodemographic and clinical data were collected and a diagnosis was issued, according to DSM-IV-TR[4]. Then, they were offered, as an alternative to the waiting list, the possibility of performing a closed MRI by previously taking an anxiolytic. Those who accepted were instructed to take 1 mg of alprazolam on the night

before the MRI, 1 mg two hours before the test and an additional 1 mg 20 minutes earlier, in the waiting room. The intervention was considered successful when the closed MRI could be performed without incidents.

Data for this study were collected retrospectively through consultation of electronic medical records.

Statistical analysis

Univariate analyses were conducted to identify factors associated with the efficacy of the intervention, using the chi-square test for qualitative variables and the t-test for continuous variables. All tests were two-tailed with a 95% confidence interval.

Results

Sample characteristics

A total of 123 patients were included, with a mean age of 54.7 (SD=13.19) years. 82 (66.7%) patients were women. 43 patients had previously been diagnosed with a psychiatric disorder, with a predominance of anxiety disorders (62.8%), followed by depressive disorders (25.6%). Only 2 patients had previously been diagnosed with claustrophobia. In the interview, it was considered that 71 patients (57.7%) met criteria for claustrophobia, while the remaining cases presented situational anxiety without criteria of claustrophobia.

Efficacy of the intervention

50 patients agreed to perform a closed MRI with a prior anxiolytic medication. In 35 of them (28.5% of the total), it was possible to successfully achieve a closed MRI. Of the remaining patients, 7 did not show up on the day of the appointment, in 6 the MRI was aborted following patient anxiety and in 2, although it was completed, the image had too many artifacts (Figure 1). The patients in whom the protocol failed (15) were again included in the open MRI waiting list. Moreover, when significant psychopathology was detected in the diagnostic evaluation, the psychiatrist recommended referral to the mental health services.

Correlates of intervention effectiveness

Only 10 patients with claustrophobia (14.1%) could complete the closed MRI successfully, compared to 25 (48.1%) of the non-claustrophobic group. The current diagnosis was the only variable with a statistically significant association with the success of the intervention ($p<0.01$). No statistically significant differences were found for the remaining collected variables (age, sex, psychiatric history).

Conclusions

The effectiveness of the intervention was considerable, especially in non-claustrophobic patients. The ability to partially alleviate the waiting list for open MRI is likely to result in shorter diagnostic procedures and lower costs. The interest is greater if one takes into account that it was a simple intervention, with a short time of medical care (about 20 minutes) and that could be generalizable to large clinical populations.

Other authors have reported a successful use of benzodiazepines to prevent anxiety symptoms during MRI. With a similar design, Klein proposed the administration of 0.5 mg of alprazolam between 60 and 30 minutes before the ap-

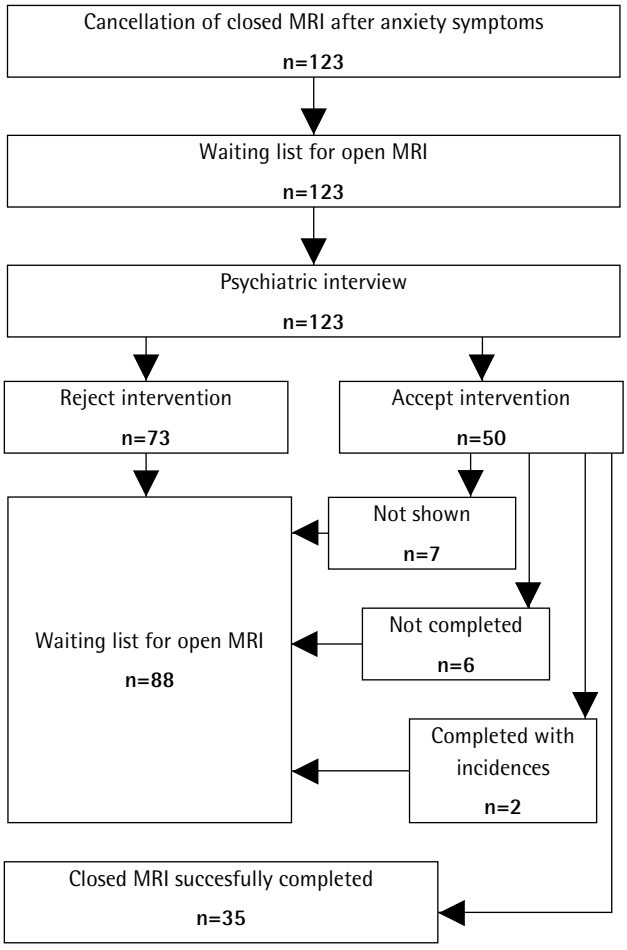

Figure 1 | *Intervention and patient flow*

pointment, and another 0.5 mg once in the waiting room[9]. With this protocol, evaluated in 100 patients, all the resonances were completed without significant adverse effects. Other authors have proposed intranasal or intravenous benzodiazepine regimens prior to MRI, with very high success rates[7,8]. It should be noted, however, that the cohorts of these studies consisted of healthy patients who had not previously suffered anxiety.

Other studies have reported a high correlation between the presence of claustrophobia and the incidence of anxiety during MRI[11]. In the present study, we found that this factor could be key to determine the suitability of repeating a closed MRI. Patients who met diagnostic criteria for claustrophobia were more likely to reject the closed MRI and, if they accepted it, were more likely not to complete the test.

A better characterization of the patients in which an MRI is prescribed would allow a more efficient use of the available resources. Special attention should be paid to claustrophobic patients. In them, it might be convenient to avoid the conscious experience of MRI, not only because of the high rates of failure, but also to avoid the suffering that comes with the claustrophobic experience. Although in the present work claustrophobia was diagnosed through a clinical interview, there are scales that allow detection by less experienced health professionals[12].

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