[a] *Centro de Salud Mental de Horta, Barcelona, Spain*
[b] *Facultad de Medicina, Universidad de Valencia, Valencia, Spain*
[c] *Departamento de Psiquiatría, Hospital Clínico Universitario de Valencia, Valencia, Spain*
[d] *Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain*
[e] *Departamento de Medicina, Área de Psiquiatría, Universidad de Oviedo, Oviedo, Spain*
[f] *Sociedad Española de Formación Sanitaria Especializada (SEFSE-AREDA), Madrid, Spain*
[g] *Facultad de Educación, Universidad del País Vasco (UPV/EHU), Bizkaia, Leioa, Spain*
[h] *Departamento de Medicina, Universidad del País Vasco (UPV/EHU), Bizkaia, Leioa, Spain*
[i] *Departamento de Psiquiatría, Hospital Universitario Cruces, Osakidetza-Servicio Vasco de Salud, Barakaldo, Spain*

* Corresponding author.
E-mail address: danielmartinez.psy@gmail.com
(D. Martinez-Uribe).

Antipsychotic consumption and diabetes mellitus. A causality analysis☆

Consumo de antipsicóticos y diabetes mellitus. Un análisis desde la causalidad

Dear Editor,

It is a fact that patients with schizophrenia run a high risk of developing metabolic problems, among them diabetes mellitus (DM). The biological mechanisms of the disorder, psychosocial repercussions and the adverse effects of antipsychotic (AP) drugs are all intermingled here.

The inference of causality is a major subject of debate in the field of epidemiology. On the one hand, different theoretical models encompass this. On the other, there is controversy over whether it is possible to demonstrate causality in an absolute manner. In epidemiology the Bradford Hill criteria are still considered as an appropriate reference to determine the possible casual association between 2 variables, since they lead to rigorous assessment of what is known and what is unknown about this possible relationship.[1]

Given the high consumption of AP, we believe it is of interest to review recent references on the relationship of these drugs with DM from the perspective of causality, using the Bradford Hill criteria to report our findings.

Strength of association

In a primary care cohort of over 200,000 people we observed a DM incidence in patients with AP which was higher than that observed in the general population (OR 1.45; 1.22–1.73). Schizophrenia did not prove to be a separate risk factor from DM.[2]

Evidence suggests that the association is higher with ''second generation'' AP (and, among them, with olanzapine and clozapine). The measurements which compare incidence (RR) or their analogues (OR) showed a mean increase in risk of 2–3 times when comparing treated patients with non treated patients or patients treated with an AP of poorer profile with one of lower hyperglycaemic capacity. When the difference of means was used it was observed that values were between 4 and 10 mg/dl of blood sugar.

Putting the Bradford Hill criteria into practice has shown that this criterion should not be reduced to the measure of association magnitude, but should include aspects such as the statistical significance or internal validity of the study. In the literature there is great disparity in presentation of the resulting event, and a lack of control on potentially important factors of confusion, such as level of psychiatric symptomatology.

Consistency

Adults with schizophrenia are the most common study group, but the development of DM from AP in adults with bipolar disorder and in children (with diverse disorders) has been observed.[3]

The growing interest in studying this issue in the child and teenage population is notable, particularly because there may be a certain lack of vigilance in this age group of this and other adverse AP effects.[4]

In the elderly, the repercussions of AP on blood sugar may be lower.[5] In diabetic patients it has been observed that taking these drugs worsens metabolic control.[6] The association between the use of AP and the development of DM has been studied using different types of designs, both observational and experimental.

Temporary sequence

A large part of the available evidence is based on cross-sectional studies, but meta-analyses and systematic reviews with longitudinal studies exist which confirm the effect of the AP.

☆ Please cite this article as: Pérez Romero C, del-Nido-Varo LP, Sarría-Santamera A. Consumo de antipsicóticos y diabetes mellitus. Un análisis desde la causalidad. Rev Psiquiatr Salud Ment (Barc). 2021;14:76–77.

Response dose effect

Correlation between plasmatic concentration of the drug (not dose administered) and the appearance of metabolic type adverse effects[7] have been described for olanzapine and clozapine.

Biological plausibility

Different biological hypotheses exist which could explain the relationship between the consumption of AP and the appearance of DM, such as the antigenic effect of serotonergic receptors, weighted increase or resistance to leptin.[8]

Reversibility

Changing AP for others of a more favourable metabolite profile leads to a significant reduction in blood sugar levels, according to a recent systematic review.[9] However, in this review only 2 clinical trials were used for analysis.

Analogy

AP have been linked to the appearance of metabolic adverse effects other than DM. Also, the induction of DM has been described as an adverse event from other pharmacological groups.

This approximation reflects how with the Bradford Hill criteria different types of evidence may be included in one setting. The effect of AP on blood sugar is, in our opinion, a fact. The medical implication of these data arises from the need to monitor this effect in all patients prescribed with AP, which today is a group represented by subjects with different sociodemographic indications and characteristics. Although the metabolic repercussion of AP could be stabilized over time,[10] long-term control is required. Given their particular vulnerability, greater efforts should be made for further control in children and teenagers.

References

1. Perrio M, Voss S, Shakir SAW. Application of the bradford hill criteria to assess the causality of cisapride-induced arrhythmia: a model for assessing causal association in pharmacovigilance. Drug Saf. 2007;30:333–46.
2. García-Fernández V, Garrido-Elustondo S, López-Rodríguez JA, Del Cura-González I, Sarría-Santamera A. [Incidence of diabetes in patients treated with antipsychotics in primary care]. Gac Sanit. 2018;32:588–9.
3. Galling B, Roldán A, Nielsen RE, Nielsen J, Gerhard T, Carbon M, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. JAMA Psychiatry. 2016;73:247–59.
4. De la Torre Villalobos M, Martin-López LM, Fernández Sanmartín MI, Pujals Altes E, Gasque Llopis S, Batlle Vila S, et al. Monitorización del riesgo cardiovascular y metabólico en niños y adolescentes en tratamiento antipsicótico: un estudio descriptivo transversal. Rev Psiquiatr Salud Ment. 2018;11:19–26.
5. Guenette MD, Chintoh A, Remington G, Hahn M. Atypical antipsychotic-induced metabolic disturbances in the elderly. Drugs Aging. 2014;31:159–84.
6. Galler A, Bollow E, Meusers M, Bartus B, Näke A, Haberland H, et al. German Federal Ministry of Education and Research (BMBF) Competence Network Diabetes Mellitus. Comparison of glycemic and metabolic control in youth with type 1 diabetes with and without antipsychotic medication: analysis from the nationwide German/Austrian Diabetes Survey (DPV). Diabetes Care. 2015;38:1051–7.
7. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry. 2009;70:1041–50.
8. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 12th edition Wiley Blackwell; 2015.
9. Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. Cochrane Database Syst Rev. 2010:CD006629.
10. Franch Pato CM, Molina Rodríguez V, Franch Valverde JI. Síndrome metabólico y antipsicóticos atípicos. Posibilidad de predicción y control. Rev Psiquiatr Salud Ment. 2017;10:38–44.

Laura Patricia del-Nido-Varo[a,*], César Pérez Romero[a], Antonio Sarría-Santamera[b]

[a] *Residente de Medicina Preventiva y Salud Pública, Escuela Nacional de Sanidad, Instituto de Salud Carlos III, Madrid, Spain*
[b] *Escuela Nacional de Sanidad, Instituto de Salud Carlos III, Universidad de Alcalá, Red de Investigación en Servicios de Salud y Enfermedades Crónicas (REDISSEC), Madrid, Spain*

* Corresponding author.
E-mail address: lnido@isciii.es (L.P. del-Nido-Varo).