

# Antibiomania after triple therapy for *Helicobacter Pylori*: Two case reports and a review of physiopathology

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**ABSTRACT – Background and Objectives:** The onset of manic symptoms in middle age requires clinicians to consider possible reversible causes, especially in patients with no previous psychiatric history. A number of drugs have been implicated as being among possible causes. The term antibiomania appeared to define cases of antibiotic-induced manic symptoms. This is a serious, but rare, adverse event. Several studies have described antimicrobial agents as being responsible for antibiomania. Our objective is to investigate the possible induction of manic symptoms by clarithromycin through two case reports and a review of the literature.

**Methods:** We report two cases of clinical manic psychotic symptoms arising in the context of treatment with triple therapy for *Helicobacter pylori* eradication. In addition, we summarize, in an unsystematic way, previously published evidence and pathophysiological mechanisms proposed.

**Conclusions:** These and other previously published cases suggest that the use of triple therapy, and especially of clarithromycin, should always be considered as a possible cause of acute manic or psychotic episode. Published evidence on the pathophysiological mechanisms is speculative so the identification and dissemination of a larger number of antibiomania cases and systematic study of them may help us to understand the underlying pathophysiological mechanisms and improve our diagnostic skills.

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## Introduction

The presence of antibiotic-associated psychiatric symptoms was described 60 years ago when several case reports of psychotic syndrome following penicillin administration emerged<sup>1</sup>. The term antibiomania subsequently appeared to define cases of antibiotic-induced manic symptoms. This is a serious, but rare, adverse event.

Regarding the number of antibiomania cases reported by the WHO and the FDA, clarithromycin seems to be the antibiotic most frequently implicated in the occurrence of this adverse effect, followed by ciprofloxacin and ofloxacin<sup>2</sup>.

The typical course of antibiomania is characterised by rapid onset of symptoms (usually within the first week of treatment) and quick, ad integrum remission after withdrawing antibiotics and administering antipsychotic medication, usually for a few days.

The aim of this paper is to report on two cases of manic episode after starting triple therapy to eradicate *Helicobacter pylori* (clarithromycin, amoxicillin and omeprazole) and to review the literature on pathophysiological mechanisms underlying this syndrome.

## Case report 1

A 54-year-old man was admitted to our hospital because of manic symptoms and behavioral disorder.

There were no previous medical or psychiatric disorders or toxic abuse reported. Nor was there a family history of mental disorders. He

had recently started treatment for *Helicobacter Pylori* (HP), taking 1 g of clarithromycin, 1 g of amoxicillin, and 20 mg of omeprazole daily. The patient took the treatment for one week, and it was completed the day before hospitalisation. He had not been treated with any other drug in the previous 3 months.

The day before stopping triple therapy, he suddenly developed manic symptoms such as insomnia, hyperthymia, tachypsychia, verbiage and hyperactivity. He also showed messianic, jealous and paranoid delusions, as well as visual and auditory hallucinations (he described having seen and heard the Virgin Mary). He was conscious, oriented, and showing transitory hypertension (210/120 mmHg) at admission, that immediately normalized after an isolated dosage of captopril 25 mg. Young mania rating scale score was 46 points and Mini-mental state examination score was 30 points out of 30. There were no other remarkable results found during physical, imaging or laboratory examinations, including Blood Analysis (BA), Electrocardiogram (ECG) and Computerized Tomography (CT).

Risperidone 3mg/d was started and the patient experienced rapid episode remission. The patient reported having taken omeprazole and amoxicillin in the past, but not clarithromycin. He was discharged 48 hours after admission with a diagnosis of Substance-Induced Mood Disorder (probably clarithromycin) and a score of 11 on the Young scale and 30/30 on the Mini-Mental State Exam (MMSE). Risperidone was maintained and gradually withdrawn over the following 10 days, verifying the absence of symptoms. Five years later, he was interviewed again. During this period, no manic or psychotic symptoms appeared. He did not take amoxicillin or clarithromycin during this period.

## Case report 2

A 47-year-old woman with no previous psychiatric or substance-abuse history was admitted to our psychiatric hospital because of behavioral disturbances and manic symptoms.

Her father was diagnosed as having a Schizoaffective disorder. Only well controlled hypertension and peptic ulcer disease were found relevant in her past medical history. She wasn't taking any regular medication.

One week before the onset of the episode, the patient was diagnosed as having an HP infection and she started taking 500 mg of clarithromycin twice daily, 1 g of amoxicillin, and 40 mg of omeprazole. Four days after starting this treatment, she suddenly developed insomnia, hyperactivity, grandiose delu-

sions, irritability, pressured speech, tangential thinking and increased energy levels. These manic symptoms persisted and escalated and she was, consequently, hospitalised.

Her physical, laboratory and imaging examinations (including BA and CT) were unremarkable. Triple therapy was discontinued and olanzapine 20 mg/day was administered from the day of admission. *One week after admission, manic symptoms still persisted (insomnia, pressure speech, tachypsychia, hyperthymia, tangential thinking), although psychotic symptoms had improved a lot. Persistence of manic symptoms forced us to add Divalproex sodium 2000 mg/day to her treatment.* She was discharged after a three-week hospital stay. She was finally diagnosed with Bipolar I Disorder, Single Manic Episode, Severe With Psychotic Features (DSM-IV-TR).

Table 1  
Comparison of clinical characteristics among case reports

	CASE REPORT 1	CASE REPORT 2
Sex	Male	Female
Age	54	47
Personal Psychiatric History	No	No
Familial Psychiatric History	No	Yes
HP treatment	Amoxicillin 1 gr Clarithromycin 1 gr Omeprazole 20 mg	Amoxicillin 1 gr Clarithromycin 1 gr Omeprazole 40 mg
Hospital stay	2 days	21 days
Treatment	Risperidone 3 mg/day	Olanzapine 20 mg/day Divalproex odium 2000 mg/day
Treatment duration after discharge	Progressive reduction Stop in 9 days	Long-Term
Restitutio ad integrum	Yes	No
Diagnosis	Substance-induced mood disorder	Bipolar I disorder, single manic episode, severe with psychotic features

HP: *Helicobacter Pylori*.

## Discussion

In both cases, there is an absence of other concurrent medications or drug abuse and a lack of previous medical conditions or personal psychiatric history in the middle age of life. Also, physical, imaging, and laboratory examinations were completely normal. We did not carry out cerebral magnetic resonance imaging, spinal tap or electroencephalography because no clinical signs or symptoms indicated doing so. Considering that both patients were conscious and appropriately oriented, delirium was ruled out; Thus, triple therapy seemed the most probable cause attending to the chronological relationship.

Since our patients received a combination of three drugs (clarithromycin, amoxicillin, and omeprazole), we have to consider the possibility that any of the three (or combinations thereof) were potentially involved in the onset of symptoms. To the best of our knowledge, there are no manic reactions associated with omeprazole described in the literature or published elsewhere. Although there are isolated reports with amoxicillin, clarithromycin is the antibiotic most commonly associated with the occurrence of anti-biomania<sup>2</sup>. Therefore, we think of clarithromycin as the most probable inducer of both manic episodes. Nevertheless, only the reintroduction of each drug separately would fairly discriminate between them in light of the recurrence of symptoms. In this sense, and in relation to case report #1, the previous use of amoxicillin and omeprazole without development of any mental disturbance strengthens our hypothesis.

There are no known interactions between amoxicillin and omeprazole, or amoxicillin and clarithromycin. Mutual interactions between omeprazole and clarithromycin have been described, showing raised levels of both drugs in blood plasma<sup>3</sup>. This situation could

lead to an increase in clarithromycin crossing the blood-brain barrier, allowing for the presence of neuropsychiatric symptoms.

Despite similarities between the two patients, some features are clearly different in the two cases and point to different diagnoses.

In the first case, negative family history for mental disorders, fast remission after withdrawal of antibiotic using low risperidone dosage, and absence of relapse after years without psychopharmacological treatment suggest a substance-induced mood disorder.

On the other hand, distinct features can be seen in the second case. There is a family history of schizoaffective disorder and slower and poorer improvement using antipsychotics after withdrawing the antibiotic, so the clinician finally required the use of a mood stabilizer. Moreover the patient did not show complete remission of symptoms after discharge and needed long-term psychopharmacological treatment. In the reported clarithromycin-induced manic episodes, a complete resolution of symptoms 24 to 36 hours after completing treatment is described<sup>2</sup>. All these features suggest the onset of bipolar disorder, possibly induced by triple therapy treatment.

In general terms, the first therapeutic approach in the presence of suspicion of anti-biomania should be the withdrawal of the drug, adding, if indicated, low doses of antipsychotics to achieve clinical remission. Although antipsychotic drugs were immediately started in both reported cases, one could argue whether symptoms would have improved just by discontinuing triple therapy. It seems possible in the first case, but not in the second one.

Persistence of symptoms despite these measures may indicate the onset of bipolar disorder. Even if complete remission is achieved, the risk of development of a true bipolar disorder should always be considered throughout the patient's lifetime.

There is little published scientific evidence on pathophysiological mechanisms and what there is speculative. This situation brings us back to the primary affective disorder pathophysiology hypothesis.

## Antibiomania physiopathology

Various proposals were found in the literature to explain the pathophysiology of this phenomenon.

– GABA: Antagonism of the GABA system has been proposed as the mechanism whereby antibiotics induce mania. The GABAergic deficit causes dopaminergic hyperactivity, especially on D2 receptors, related to the appearance of positive symptoms in schizophrenia. Quinolones competitively inhibit the binding of GABA to its receptors<sup>4</sup> and Isoniazid decreases GABA-mediated transmission, increasing levels of neurosteroids in the CNS<sup>5</sup>. Nevertheless, we did not find any evidence in the literature of a possible effect of clarithromycin or amoxicillin on the GABA system.

– CORTISOL: Alterations in cortisol level underlying depression and mania are well known. An elevation of cortisol levels in patients with acute manic episode has been described<sup>6</sup>.

Rifampicin has been related to altered Dexamethasone suppression tests in patient with affective disorders<sup>7</sup>. It has been reported that rifampicin induces adrenal crises in patients with Addison's disease on corticosteroid replacement therapy<sup>8</sup>. Rifampicin may accelerate corticosteroid metabolism and clearance, thanks to CYP3A4 induction and to increased urinary excretion of 6-hydroxycortisol<sup>9,10</sup>. Moreover, Rifampicin was proposed as a possible trigger of glucocorticoid

receptors (GR)<sup>11</sup>, which could explain the adverse effects of the drug on the CNS. Nevertheless, another study failed to demonstrate GR activation by rifampicin in some tissues afterwards<sup>12</sup>.

Macrolides, such as clarithromycin, slow glucocorticoid clearance<sup>13</sup>. Concomitant use of clarithromycin results in a significantly higher plasma concentration and a 65% reduction in methylprednisolone elimination<sup>14</sup>.

– GLUTAMATE: It has been postulated that macrolides may cause psychosis-like symptoms due to their inhibitory action on the glutamate system through NMDA receptors in the CNS<sup>15</sup>.

– PROSTAGLANDINS: Increased levels of PGE1 in patients with manic episodes have been described. Lithium normalises PGE1 levels inhibiting its precursor, dihomo-gamma-linolenic acid<sup>16,17</sup>. PGE-1 is related to calcium uptake regulation and intracellular release. They are crucial to nerve conduction mechanisms and regulation of transmitter release<sup>18</sup>. There is increasing interest in the relationship between the arachidonic acid system (AA) and the pathophysiology of bipolar disorder. It has been described as an AA pathological excess, along with an increase in PGE2, its final product, in bipolar disorder<sup>19</sup>. The therapeutic action of anti-manic-mood stabilisers (lithium, carbamazepine and valproate) is related to decreased AA and PGE COX-2 cerebral release<sup>20</sup>. On the other hand, other authors have not observed such a relationship between levels of PGEs and mania<sup>21,22</sup>.

Several studies suggest that a wide range of antibiotics (some quinolones, cephalosporins, tetracyclines, rifampicin, clindamycin and some macrolids including clarithromycin) could modify levels of PGE-2 in several tissues<sup>23-33</sup>.

– OTHER PROPOSITIONS: There is growing evidence on several intracellular pathways involved in bipolar disorder pathophysiology, including the Akt and Wnt system, through GSK-3B protein. The therapeutic effect of lithium and valproate has been linked to its GSK-3B inhibition<sup>34-36</sup>. The macrolide rapamycin could act through inhibition of epileptogenesis, as well as its action on Akt and GSK-3b mTORC and on mitochondrial protein synthesis<sup>37</sup>. To the best of our knowledge, there is no similar evidence regarding clarithromycin or amoxicillin.

There is also growing information suggesting that individual genetic factors could play a role in the risk for developing neural side effects of a drug<sup>38</sup>. There is no published evidence regarding antibiomania, but this possibility might help in the understanding of this phenomenon in the future.

It has recently been suggested that gut microbiota could play a role in maintaining homeostasis in health and contributing to the pathogenesis of some diseases, including depression. In fact, some information points to a possible different pattern of gut microbiota in depression and stress-models in animals<sup>39</sup>. The term “psychobiotics” has recently been coined to denote live organisms (e.g., probiotics) that, when ingested in adequate amounts, could improve some mental health diseases. Preclinical work suggests that certain psychobiotics possess antidepressant activity in animal models. Effects are thought to be mediated via the vagus nerve, spinal cord, or neuroendocrine systems<sup>40</sup>. Although this is highly hypothetical, as short-treatment with clarithromycin produces modifications of the gut microbiota immediately after treatment<sup>41</sup>, one may speculate that these changes may be a possible explanation for the mood disturbances in antibiomania.

## Conclusions

Most antibiomania cases are relatively recent. This could be because this adverse effect is more common among newer antimicrobials, but could also be explained by the current emphasis on adverse effects and greater knowledge of them.

These and other previously published cases suggest that the use of triple therapy, and especially of clarithromycin, should always be considered as a possible cause of acute manic or psychotic episode. Published evidence on the pathophysiological mechanisms is speculative so the identification and dissemination of a larger number of antibiomania cases and systematic study of them may help us to understand the underlying pathophysiological mechanisms and improve our diagnostic skills.

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