



## Etiology, drugs and incidence in Cotard syndrome

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### ABSTRACT

This study aimed to perform a literature review about Cotard's syndrome, or delusions of negations (as it is also called). Data collection was based on the following search websites: Science Direct, Web of Science, PsycINFO, Medline, PubMed, Lilacs and Scielo, without limit time between publications. All papers found in review literature, in total 297, were selected and analyzed. In according with results, it was possible to organize a general survey about this very rare syndrome, discussing their symptoms, probable etiology, neurochemical processes involved, clinical diagnosis and treatment. In addition, it was also possible to construct a list of the most commonly prescribed drugs by psychiatrists, including per day dosage administered and the pharmacological class. In this view, it was observed among these most prescribed drugs, antidepressants represent the main class employed in treatment of these patients. After statistical analysis, it was observed the incidence of this syndrome in reported cases, using sex and age as variables, showing a great incidence upon female individuals between 50 and 59 years old.

**Key words:** Cotard, Cotard syndrome, Délire des negations, Delirium of Negations

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### INTRODUCTION

Jules Cotard was born on June 1<sup>st</sup> 1840s, in Issoudun, France. He studied medicine in Paris, and always showed interesting in pathologies that affected the central nervous system (CNS) [1,2]. During years, he studied melancholia, which it was associated with a specific delirium type, namely “*délire des negations*” (term from French) [3].

The first case described by Jules Cotard, at *Société Medico-Psychologique* meeting, in 1880s, referred to a patient who claimed not to have brain, nerves and viscera, being only composed by skin and bones [1,4-7]. In addition, this patient said did not need to eat, because she believed in her own immortality [1,5].

Then, Cotard believed had found a new psychosis type, characterized by anxious melancholy, condemnation ideas or demonic possession, suicidal behavior, insensibility to pain, immortality feeling, and delusion of non-existence involving own body or just some parts. All observations led to a new term in psychiatric area, called *Cotard's delirium* [1,5] which during a long time was called *Delirium of negations*. This term was applied to cases of patients with negation symptoms, including the own existence and outside world [1,2,5,8-14]. Often, these patients claimed to be a parallel spectral reality around the “*real world*”, lying in hell or *Gehenna* (biblical valley near Jerusalem, which represented the purgatory, known as the Valley of the Son of *Hinnom*) [15].

In 1884, Cotard has observed that the first symptom presented in patients affected by this disorder would be a reduction of “psychomotor energy.” This reduction would lead to a psychomotor retardation and image memory loss (for common objects) and later progressing to delusion of negations [1].

Cotard's syndrome generally is defined as a *nihilistic* delusion [7,10,16-20] in which the patient claims to be dead or be paradoxically immortal [9,15,21-32]. In addition, the patient can affirm that has no soul, his biological functions are not supported, or is dismembered or internally decomposed [2,28,30,31,33]. In many cases, the patient might experience an olfactory hallucinations type and/or kinesthetic [34], with constant complaints as exposure to the decomposition of the his body or absence of organs [3,35]. Some patients claim to smell the odor from his own "decomposition" [32].

The expressions "undead" [34] or "syndrome of walking cadaver" [35] also are nomenclatures for classify the Cotard's syndrome. Terms that seem to allow a junction between the body's decomposition and immortality ideas, that can occur in Cotard's syndrome, simultaneously.

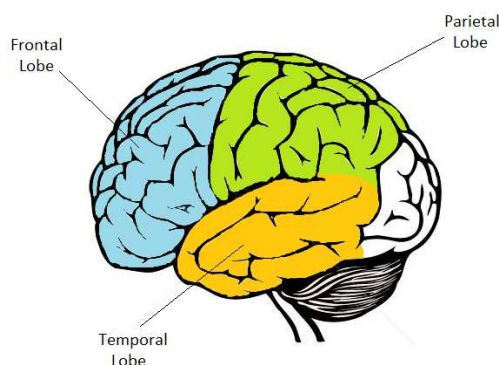
There are also reports of patients that may have difficulty recognizing people nearby, familiars and friends (non-recognition of their faces), similar to what happens in cases of Capgras syndrome [11,15,32]. For differential diagnosis in these cases should be considered the patient's complaint, noting the reasons that lead to the non-recognition of faces. Generally, the patient with Cotard say that can not recognize faces because he is "dead" and/or "invisible" to his familiars/friends. In cases of Capgras, the patient believes that his familiars/friends are impostors physically identical to the "true familiars/friends" [5].

Cotard's syndrome can occur in young or elderly people, but is observed a higher prevalence in young women [26], and in most cases, it is associated with major depressive episodes [7].

Considered a rare syndrome and origin still little explored. In general, it occurs as a set of secondary symptoms to other psychiatric disorders such as, psychotic depression, schizophrenia and bipolar disorder [36-39]. In some cases, it is associated with the presence of guilt over something that happened in the past [24].

This syndrome may also be associated with particular neurological conditions, able to leave vulnerable persons to appearance of the syndrome, such as neurosyphilis, multiple sclerosis, cerebrovascular disorders, post-traumatic brain injuries [15,30,40] and dementia [41].

Neuroimaging studies using Single-Photon Emission Computed Tomography (SPECT)x suggest that the etiology of this syndrome is associated with dysfunction of the frontal, temporal and parietal lobes (Figure 1) [30-32,40,42] of the non-dominant hemisphere of the brain of patients [2,11,43]. This last is related to feelings of "inner emptiness", absence and death [30].



**Figure 1. The most important lobes from brain involved in Cotard's syndrome etiology**

Another hypothesis suggests that the syndrome of Cotard is caused by a disconnect between temporal cortex and limbic system [32], as well as all sensory areas contained in the limbic system, which would lead to a complete loss the emotional contact with outside world [11].

Some studies relate the appearance of symptoms of Cotard with the abuse of ecstasy [44]. However, there is still no consensus on the etiology of the Cotard's syndrome.

In some neurochemical studies in brains from Cotard's patients was observed that there is a hyperactivity of two neurotransmitters involved in various biological functions: dopamine and norepinephrine [7,45].

In blood plasma samples from patients were observed high levels of metabolites such as homovanillic acid (HVA), dopamine metabolite, and 3-methoxy-4-hydroxyphenylglycol (MHPG), norepinephrine metabolite [7].

The formation of HVA can occur by two pathways involving the same enzymes. First route, initially the dopamine undergoes action of the monoamine oxidase enzyme (MAO), which converts the amine group (R-NH<sub>2</sub>) in a carboxylic acid group (R-COOH). Then the catechol acid formed undergoes the action of catechol-*O*-methyltransferase enzyme (COMT), generating HVA. In second route, the dopamine may suffer initially action of COMT and, subsequently, MAO (Figure 2) [46].

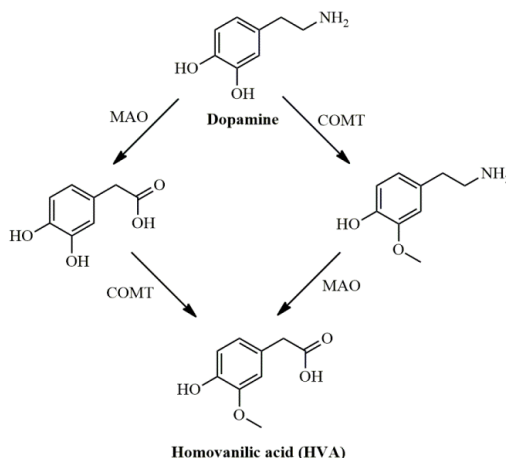


Figure 2. Homovanillic acid (HVA) formation from dopamine metabolism

The formation of MHPG occurs through different pathways involving the same enzymes which metabolize dopamine (COMT and MAO), however the aldehyde reductase enzyme plays an important role in the formation of this metabolite, this has the function of reducing the aldehyde group (-CHOR) from intermediate metabolite in a hydroxyl group (R-OH) (Fig. 3) [47].

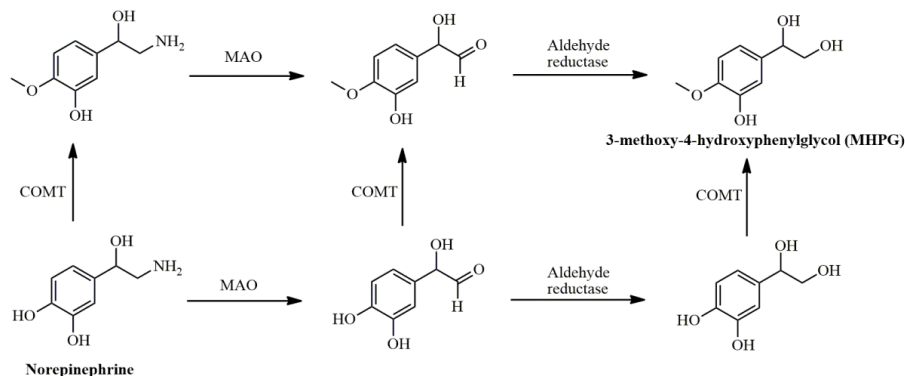


Figure 3. 3-methoxy-4-hydroxyphenylglycol (MHPG) formation from norepinephrine metabolism

In studies using SPECT was verified that the main receptor involved in Cotard's syndrome is D<sub>2</sub> dopaminergic receptor, also observed especially in a patient schizophrenics [48].

## EXPERIMENTAL SECTION

Literature review was performed through specialized research databases (SCIENCE DIRECT, WEB OF SCIENCE, PSYCINFO, MEDLINE, PUBMED, LILACS, and SCIELO) using different combinations of the following keywords: "Cotard", "Cotard Syndrome", "Délire des Négations", "Cotard Delusions" and "Delirium of Negations". The manuscript selection was based on inclusion criteria: articles published with keywords in the title. There was no restriction concerning the publication periods and only the works reviewed by pairs were selected. For the selection of the manuscripts, two independent investigators first selected the articles according to title, then to abstract, and then through an analysis of the full-text publication. The resulting articles were manually reviewed with the goal of identifying and excluding the works that did not fit the criteria described above.

## RESULTS AND DISCUSSION

In total, 297 articles were obtained from literature search step, 59 articles met the selection criteria, being 47 articles selected for statistical studies and graphical creation. The study selection process is shown in Figure 4. Most of the selected articles were report case studies.

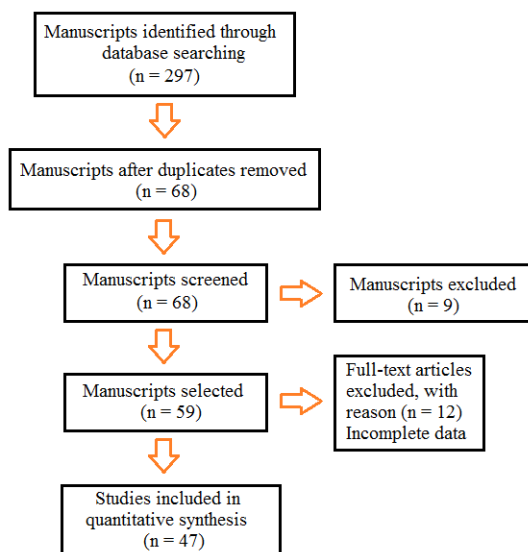


Figure 4. Workflow diagram the search process for selection of studies

#### The Most Prescribed Drugs in Cotard's Cases

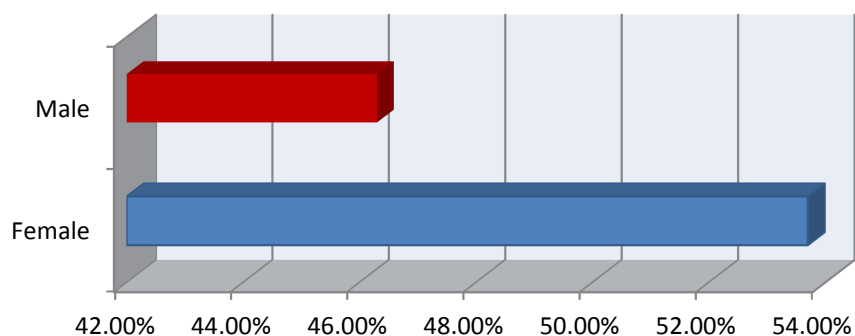
Several times antipsychotics benzodiazepines antagonists of dopamine receptors have been shown as effective alternative for treatment of patients with Cotard [15,31]. Among the most used atypical antipsychotics, from benzodiazepine class, can be cited the olanzapine [31,32]. In Table 1, are listed the most commonly used drugs in the treatment of these patients.

Table 1. Drug classes used in the treatment of the Cotard's syndrome.

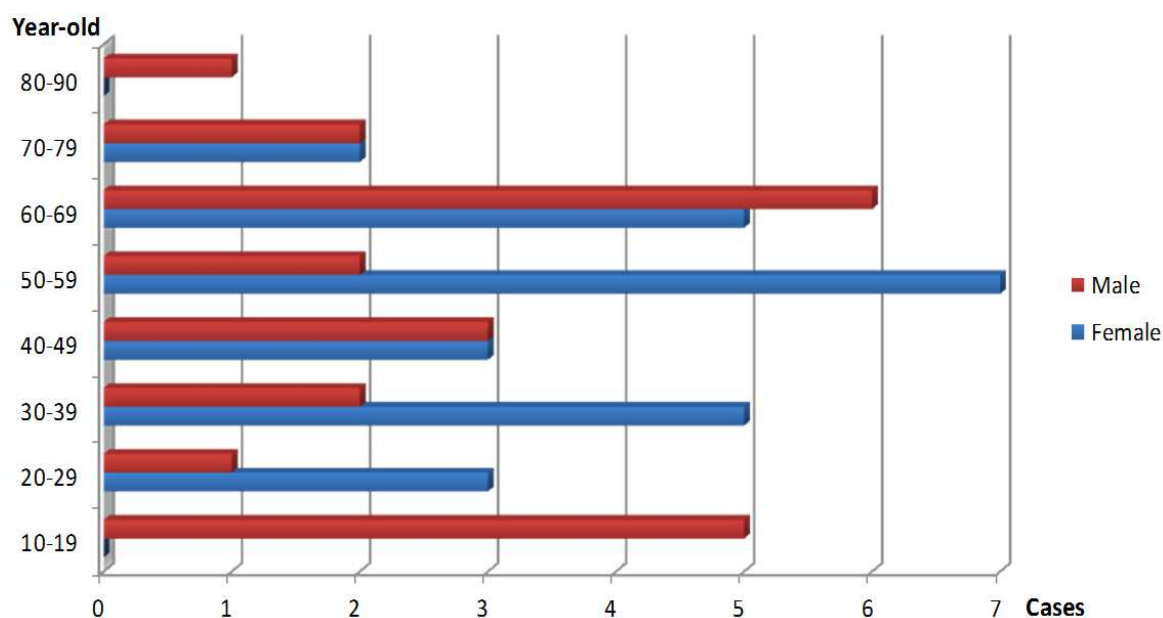
Drug	Class	Dose/day	Reference
Alprazolam	Ansiolytic	0.25 mg	[6,49]
Amisulpiride	Atypical Antipsychotic	100 mg or 600 mg	[31,50]
Amitriptiline	Antidepressant	25 mg	[16]
Amoxapine	Antidepressant	50-90 mg	[7]
Aripiprazole	Atypical Antipsychotic	10 mg	[51]
Chlorpromazine	Typical Antipsychotic	50 mg	[20]
Citalopram	Antidepressant	20 mg	[20,31]
Clonazepam	Ansiolytic/ Anticonvulsant	0.5 mg	[52]
Duloxetine	Antidepressant	60 mg	[49]
Escitalopram	Antidepressant	15 mg or 20 mg; or 30 mg	[6,49,53,54]
Fluoxetine	Antidepressant	40 mg	[17,45]
Flupentixol	Typical Antipsychotic	3 mg	[16]
Fluvoxamine	Antidepressant	100 mg or 200 mg	[48]
Haloperidol	Typical Antipsychotic	10 mg or 15 mg	[17,31,38]
Imipramine	Antidepressant	25 mg or 50 mg	[31,48]
Lorazepam	Ansiolytic	2 mg or 2.5 mg or 4 mg	[6,31,49,50,53]
Mianserin	Antidepressant	90 mg	[31]
Mirtazapine	Antidepressant	30 mg	[6,31,50]
Olanzapine	Atypical Antipsychotic	10 mg or 25 mg	[6,31,50,53,54]
Paroxetine	Antidepressant	10 mg	[7]
Perphenazine	Typical Antipsychotic	150 mg	[55]
Quetiapine	Atypical Antipsychotic	600 mg	[17,33]
Risperidone	Atypical Antipsychotic	4 mg or 6mg	[45,49]
Sertraline	Antidepressant	100 mg	[6,17,50,52]
Sulpiride	Atypical Antipsychotic	300 mg or 600 mg	[17,38]
Tranlycypromine	Antidepressant	60 mg	[33]
Trimipramine	Antidepressant	150 mg	[55]
Venlafexine	Antidepressant	150 mg or 225 mg	[6,17,31,50]
Zolpidem	Hypnotic/ Antidepressant	10 mg	[20]

**Statistical Data Obtained from Case Reports**

After all analysis of case reports in the literature, in total 47, was observed that this syndrome has higher incidence among female subjects, totaling 53.7% (Graphic 1), between 50 and 59 years old. In addition, the higher incidence among men was observed between 60 and 69 years old (Graphic 2).



Graphic 1. Female and male proportion found in case reports



Graphic 2. Years-old of patients in case reports

Overall, this syndrome does not yet have its own symptoms that characterize as an independent psychopathology, given its association with several pathologies. However, the ideas set by patients and experimented hallucinations could easily lead to a uncorrect diagnosis of this syndrome [25].

The most used tests in suspected cases are: electromyography, nerve conduction velocity testing and magnetic resonance imaging [45]. This last, in specific cases, can reveal atrophy of the brain insular cortex, which is related to the symptoms of nihilism observed in patients [56].

The treatment of this disorder by electroconvulsive therapy (ECT) has been used since 1960 [50], and has proven to be an efficient alternative when pharmacological treatment is not effective [37,53,57-59] or in chronic stage patients [45].

Regarding graphic 2, the number of cases diagnosed in relation to predominant age group, first, among women, the predominant age of incidence of the disease was between 50 and 59 years old. Second, it was observed that the age range from 30 to 39 years old, also represents a significant bearing phase, among women.

Among men, the highlight was the age group from 60 to 69 years old with various numbers of identified cases. It also can be observed that the age group ranging from 10 to 19 years has occupied the second place as the most prominent age group of occurrence for this disease among men.

These data attract attention because they suggest a wide variation in age group of occurrence for this disease, especially among men, which to be focused on part of childhood, adolescence and maturity. In relation to women, this change was to a lesser extent, as this incidence focused on adulthood and early maturity. Assuming 70 until 79 years old, was noted a balance between the incidence number in men and women, which did not suggest to significant differences within sex and age group variables.

### CONCLUSION

Research has shown that Cotard's syndrome refers to a disease still little known, and whose main characteristic is the presence of delirium of negations. Accordingly, the individual tends to deny its own existence and the existence of the world around them. Other symptoms may also be observed, as the belief in immortality, the presence of decay and dismemberment ideas, guilt and nihilistic delusions. Its etiology is still little explored, but points to some hypothesis, as the presence of facilitators neurological conditions, parts of the brain dysfunction or disconnection between the temporal cortex and the limbic system. Among the most widely used for the treatment drugs are benzodiazepines, antipsychotics and anxiolytics. In extreme cases, electroconvulsive therapy has also been shown as an effective alternative. The prevalence of reported cases in the literature showed that women are more vulnerable in 53.7% of cases, compared to men (46.3%). In terms of age, for women, the most prevalent age group was 50 to 59 years old. Among men, the age group from 60 to 69 years old is that stood out with the highest number of cases identified in the literature. Furthermore, the analysis of all this information generated some important points: (1) the complexity of the phenomenon, which often appears as a kind of secondary disease to other more well-known disease, lacking often a differential diagnosis for its demarcation; (2) the difference between the genders should be considered, as well as the most prevalent age group between the sexes because the treatment must take into consideration such information; (3) the need for new studies that explore more deeply the neurochemical perspective of the functioning of this disease, so that new pharmacological treatment options can be made possible.

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