

# MAY THE BEST FRIEND BE AN ENEMY IF NOT RECOGNIZED EARLY

## Possible role of omega-3 against cardiovascular abnormalities due antipsychotics in the treatment of autism

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**Abstract** – Autism spectrum disorders (ASD) are neurodevelopment disorders that cause severe and pervasive impairment in socialization, communication, and behavior. Although the availability of antipsychotic treatment in ASD has expanded, we will be very careful with side effects of these pharmacological agents. Following this reasoning, emerging data indicate that some antipsychotics may be associated with cardiovascular adverse events (e.g., QT interval prolongation), suggesting that this could be correlated to sudden death. Quite interesting, substantial evidence from epidemiological and case-control studies indicates that omega-3 reduces the risk of cardiovascular mortality, particularly sudden cardiac death. In accordance to the above mentioned findings, as omega-3 fatty acids *per se* have a direct cardiovascular protective role, our paper hypothesized that omega-3 fatty acids supplementation in ASD patients treated with atypical antipsychotic drugs may reduce cardiac arrhythmias and hence sudden cardiac death.

KEY WORDS: autism spectrum disorders, heart, sudden death, omega-3.

### Pode um melhor amigo ser um inimigo se não reconhecido a tempo: possível papel do ômega-3 nos efeitos cardiovasculares secundários ao tratamento antipsicótico de pacientes com autismo

**Resumo** – As desordens do espectro autista (DEA) são um grupo de doenças do desenvolvimento que causam um grave comprometimento na socialização, comunicação e comportamento. Embora o tratamento na DEA com drogas antipsicóticas tenha se expandido, é necessária a observação cuidadosa de efeitos colaterais destes fármacos. Nesta linha, dados recentes têm associado o uso de antipsicóticos com efeitos adversos cardiovasculares (como prolongamento do intervalo QT), sugerindo que possa haver uma correlação com morte súbita. Evidências originadas em dados epidemiológicos e estudos de caso-controle indicam que o Omega-3 reduz o risco de mortalidade por causa cardiovascular, particularmente a morte súbita de origem cardíaca. Concordante com estes achados, como o Omega-3 *per se* tem um papel protetor cardiovascular direto, nosso artigo levanta a hipótese que a suplementação de ácidos graxos Omega-3 em pacientes com DEA tratados com drogas antipsicóticas podem reduzir o risco de arritmias cardíacas e assim a morte súbita cardíaca.

PALAVRAS-CHAVE: desordens do espectro autista, coração, morte súbita, ômega 3.

#### AUTISM: GENERAL ASPECTS

Autism spectrum disorders (ASD) are neurodevelopmental disorders that cause severe and pervasive impair-

ment in socialization, communication, and behavior<sup>1,2</sup>. These include poor eye contact, deficits in other non-verbal social behaviors, social withdrawal, impaired so-

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cial reciprocity, echolalia, motor stereotypes, intense and circumscribed interests, and a preoccupation with parts of objects instead of the whole<sup>1,2</sup>. These disorders are usually first diagnosed in early childhood and range from autistic disorder, through pervasive development disorder not otherwise specified, including Asperger syndrome<sup>2</sup>. The ASD are more common in the pediatric population than are some better known disorders such as diabetes, spinal bifida, or Down syndrome<sup>3</sup>. Prevalence studies have been done in different populations, including USA, United Kingdom, Europe, and Asia. A recent study of a U.S. metropolitan area estimated that 3.4 of every 1,000 children 3-10 years old had autism<sup>4</sup>. The specific cause of autism is unknown, however, evidence from twin and family studies indicates that autism is highly heritable<sup>1</sup>, neurochemical investigations have identified abnormalities in monoamines, glutamate,  $\gamma$ -amino hydroxybutyrate, and neuropeptides<sup>1,5</sup>, functional neuroimaging studies are beginning to demonstrate differences between the brains of persons with autism and those of controls<sup>1,6</sup> and brain regions potentially involved in autism and related disorders are diverse and include the amygdale, cerebellum, fusiform gyrus, and prefrontal cortex<sup>1,7</sup>.

Although the availability of antipsychotic treatment in ASD has expanded, we should consider it very careful because of these pharmacological agents' side effects. In these way, emerging data indicate that some antipsychotics may be associated with cardiovascular adverse events (e.g., QT interval prolongation), suggesting that this could leads to torsade the points or sudden death<sup>8</sup>. Quite interesting, substantial evidence from epidemiological and case-control studies indicates that omega-3 reduces the risk of cardiovascular mortality, particularly sudden cardiac death<sup>9</sup>. In accordance to the above mentioned findings, as omega-3 fatty acids *per se* have a direct cardiovascular protective role<sup>9,10</sup>, we hypothesized that omega-3 fatty acids supplementation in ASD patients treated with atypical antipsychotic drugs may reduce cardiac arrhythmias and hence sudden death.

#### **OMEGA-3 AND CARDIOVASCULAR SYSTEM: ANTIARRHYTHMIC PROPERTIES AND PREVENTION OF SUDDEN CARDIAC DEATH**

The beneficial effects of omega-3 fatty acids in the cardiovascular system have been described since the seventies. Dyerberg and Bang<sup>11</sup> demonstrated that the low prevalence of cardiac diseases in Eskimos might probably be due to high dietary ingestion of omega-3 fatty acids. In the same decade, a number of experimental studies showed an antiarrhythmic role of the omega-3 fatty acid<sup>12</sup>. In this line, McLennan and Charnock, two Australians researchers, conducted several experiments to confirm the possible antiarrhythmic role of omega-3. Initially, it was

demonstrated that a dietary composed from fish oil (tuna) could prevent the ventricular fibrillation in rats induced by coronary artery occlusion following reperfusion<sup>13,14</sup>. Subsequent studies confirmed their previous data<sup>15,16</sup>. Bilman and colleagues using a sudden cardiac death model in dogs observed a reduction of arrhythmias and sudden cardiac death following ischemia induction after omega-3 administration<sup>17,18</sup>. Moreover, several works demonstrated positive effects of omega-3 in arrhythmia reduction<sup>19-23</sup>. The antiarrhythmic mechanism induced by omega-3 was modulated by  $\text{Na}^+$  and  $\text{Ca}^{2+}$  currents in cardiac cells<sup>24</sup>. In the same way, positive effects of omega-3 have been also observed in clinical studies. Accordingly, several studies in the nineties demonstrated that fish consumption, 1 or 2 times per week were associated to a 50% reduction of sudden cardiac death<sup>25,26</sup>. Furthermore, a clinic study for infarct prevention conducted by an Italian group (*GISSI-Prevenzione*), using an dose of 850 mg/day de omega-3 in 11324 subjects presenting a first myocardial infarction episode, observed a significant reduction of death caused by cardiovascular complications (30%) as well as in sudden death (45%) when compared to control subjects, suggesting an antiarrhythmic role of omega-3<sup>27,28</sup>. In conclusion, human and animals studies have demonstrated a possible action of omega-3 in the prevention of cardiovascular abnormalities and reduction of occurrence of sudden cardiac death.

#### **ATYPICAL ANTIPSYCHOTICS DRUGS, AUTISM AND CARDIOVASCULAR ABNORMALITIES**

Antipsychotic therapy has become indispensable in the treatment of a variety of symptoms in ASD<sup>1</sup> and several evidences shows that atypical antipsychotics are considered more effective than conventional antipsychotics in treating certain symptoms associated with ASD, such as aggression, irritability, and self-injurious behavior<sup>29</sup>. In these lines, the atypical antipsychotics risperidone, olanzapine, quetiapine and ziprazidone are the most commonly prescribed for ASD<sup>1,29</sup>. Concerning risperidone, several studies shows that this psychotropic atypical antipsychotic agent offers a valuable emerging option for the treatment of irritability associated with autistic disorder in children and adolescents<sup>30</sup>. Olanzapine and quetiapine have shown minimal clinical benefit in ADS based on clinical trials published at the moment<sup>1,29</sup>. Concerning ziprazidone, the use of this atypical antipsychotic in ASD remains limited, however, a single case series of 12 patients aged 8-20 years found improvements in the areas of aggression, agitation, and irritability, suggesting a future promise as a treatment for adolescents with ASD<sup>31</sup>.

In accordance to this reasoning, a pertinent question could be evaluated: should the physician pay more attention with possible cardiac abnormalities during atypical

antipsychotic treatment in ASD? Although the incidence of serious adverse cardiac events in response to atypical antipsychotic medications is relatively low, some considerations should be made. For example, Ravin and Levenson described a patient who developed fatal pulseless electrical activity following initiation of risperidone therapy, suggesting that prolongation of the QTc interval with severe adverse effects remains a possibility with the use of this atypical antipsychotic<sup>32</sup>. Recently, Janion and colleagues<sup>33</sup> reported a case of a 53 year old female with olanzapine-induced QT interval prolongation and fatal ventricular fibrillation, suggesting that all antipsychotic drugs have the potential for serious adverse events. In 2004, Kurt and Maguire called our attention about the risk of QTc interval prolongation associated with quetiapine administration<sup>34</sup>. They related a 14-year-old boy who ingested 1900 mg of quetiapine. One and one half hours after ingestion, the QTc interval lengthened from 453 msec to 618 msec on the printout (manual calculation was 444 msec to 500 msec, respectively), suggesting a relationship between higher doses of quetiapine, higher serum levels and the propensity for QTc interval prolongation. Concerning ziprasidone, Posey and co-workers<sup>1</sup> related in an elegant review article, the potential for QTc interval prolongation with this drug on electrocardiography led to a warning in the full prescribing information. The authors suggested that ziprasidone should not be given to individuals with cardiac arrhythmias or long QT syndrome or who take other medications that can prolong the QTc interval.

**CONCLUSIONS AND FUTURE REMARKS**

As related before, emerging data indicate that some atypical antipsychotics prescribed for ASD may be associated with cardiovascular adverse events (e.g., QT interval prolongation), suggesting that this could lead to torsade the points or sudden death<sup>8</sup>. Although the availability of pharmacological treatment of ASD has expanded, the atypical antipsychotic drugs are still limited in clinic efficacy<sup>1</sup>. In these lines, several factors such as genetic, environmental and social can contribute to the inefficacy of therapeutic outcome patients with ASD. Among these factors, nutritional aspects, i.e., omega-3 fatty acids deficiency should also have an interesting role in this scenario. In accordance to these findings, as omega-3 fatty acids *per se* have a direct cardiovascular protective role (e.g., reduce serum triglycerides levels, cardiovascular disease prevention, antiarrhythmic effects, treatment after a myocardial infarction, and secondary prevention of cardiovascular disease)<sup>9,10</sup>, we believe that omega-3 fatty acids fatty acid supplementation in patients with ASD and treated with atypical antipsychotics may reduce cardiac arrhythmias and hence sudden death. In parallel, it is interesting to note that this hypothesis was evaluated by our and others

research groups in schizophrenia<sup>35,36</sup>, one of the most severe forms of mental illness associated with an increased risk of cardiac sudden unexpected death and which patients make use of antipsychotics drugs. For instance, in a dose-ranging exploratory study of eicosapentaenoic acid (EPA) in 115 patients treatment-resistant schizophrenia (31 on clozapine, 48 on new atypical drugs and 36 on typical antipsychotics), subjects received 1, 2 or 4 g/day of adjunctive EPA or placebo for 12 weeks<sup>37</sup>. In patients on clozapine, a clinically important and statistically significant effect of EPA was noted (greatest effect at 2 g/day)<sup>37</sup>. Improvement correlated positively with a rise in erythrocyte arachidonic acid (AA) concentration. Additionally, clozapine-treated patients who received EPA 2 and 4 g/day showed significant reduction in triglyceride levels that were elevated previously during clozapine use<sup>37</sup>.

In the general population, clinical studies of omega-3 fatty acids have shown a reduction in sudden cardiac death, suggesting that omega-3 may have antiarrhythmic effects<sup>38</sup>. Moreover, a relationship between red blood cell (RBC) membranes omega-3 fatty acids levels and risk for sudden cardiac death have been reported as well<sup>39</sup>. Similarly, deficits in red blood cell omega-3 fatty acids have been reported in medicated psychotic subjects<sup>41,49</sup>. Quite interesting, compelling evidence was found that a low dietary of omega-3 fatty acids in conjunction with sedentary behavior and mental stress combined with various personality traits can enhance sympathetic activity and increase the secretion of catecholamine, cortisol and serotonin, all of which appear to be underlying mechanisms involved in metabolic syndrome<sup>42</sup>, a potentially catastrophic multiplex risk factor for cardiovascular disease and hence sudden cardiac death in patients prescribed with antipsychotic drugs.

Concerning specifically the pediatric population, Vancassel et al. in an elegant study demonstrated a reduction in polyunsaturated fatty acids and aradonic acids in

*Table. Primary dietary source of omega-3 fatty acids. Adapted by permission of Dr. Marianna Mazza<sup>45</sup>.*

Fish oils	Plant oils
Salmon	Flaxseeds
Mackerel	Flaxseed oil
Halibut	Canola (rapeseed) oil
Sardines	Soybeans
Herrings	Soybean oil
Anchovies	Pumpkin seeds
Tuna	Pumpkin seed oil
Oyster	Purslane
Lobster	Walnuts

ASD and in mentally retarded patients, when compared to normal patients. Similar variations have been described in other psychiatric diseases, such as schizophrenia, attention deficit and hyperactivity disease, major depression and bipolar disorders, compared to control subjects<sup>43</sup>. The authors proposes this could represent an additional approach to the treatment of autism, through polyunsaturated fatty acids dietary supplementation<sup>43</sup>. Other authors, in a pilot study suggested the effectiveness of fish oil supplementation to reduce hyperactivity in 12 children with ASD. Considering this data together, it seems that polyunsaturated fatty acids serum levels may play an important role in the mechanisms of development of behavioral diseases<sup>44</sup>.

Where do we go from here? We are sure that more needs to be done and on the basis of laboratory data and clinical findings, there are reasons to suggest that omega-3 may offer a host of benefits to people with ASD. As we know, omega-3 fatty acids are long-chain, polyunsaturated fatty acids found in plant and marine sources<sup>45</sup> (Table). Actually, it has long been believed that a daily intake of 3000 to 4000 mg of fish oil supplements or 2 to 3 servings of fatty fish per week are safe and effective to adults in general, included those with psychiatric disorders<sup>45</sup>. In this way, new considerations and experimental, epidemiological and clinical studies should be evaluated to establish with precision the relationship between omega 3 fatty acids, atypical antipsychotic and ASD.

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