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The Risks of Using 2,4-Dinitrophenol (2,4-DNP) as a Weight Loss Agent: A Literature Review

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1. Abstract

The prevalence of obesity has steadily increased in response to changes in diet and physical activity patterns over the past 10 years, becoming one of the leading causes of morbidity and mortality worldwide. In addition, the popularity of social networks has increased social and cultural pressure for the search for the "perfect body". These factors result in the search for fast and unconventional methods of weight loss, such as the use of weight loss accelerating drugs. 2,4-Dinitrophenol (2-4-DNP or DNP) is an industrial chemical used to lose weight quickly. Due to its great potential for toxicity, its use has been banned in several countries since 1938. However, it is still possible to have access to this drug, mainly through the internet, which has increased cases of intoxication and death. Despite several case reports on the dangers associated with DNP, scientific works on the subject are still scarce, highlighting the need to disseminate information on the subject. In this context, the aim of the present study was to carry out a literature review on DNP and analyze case reports of its use as a weight loss agent and the associated risks. For this, articles from three electronic databases (Scientific Electronic Library Online (SciELO), National Library of Medicine (MEDLINE) and Google Scholar) were selected. Thirteen works dating from 2004 to 2021 were included. The selected works addressed reports of cases of intoxication, overdose and death caused by the use of the drug in order to lose weight. Articles that did not meet the inclusion criteria were discarded. As a result, it was found that the main users of the drug are young adults and mostly male. It was also found that despite the ban on its use, DNP is still easily accessed and its potential for toxicity is extremely high, since most of the intoxicated patients died. Therefore, it is necessary to raise awareness and spread information about the true risks associated with the consumption of DNP.

2. Introduction

Obesity is now a global public health problem and its incidence has grown in recent decades (Blüher, 2019). As obesity is a chronic, complex disease of multifactorial etiology, influenced by genetic, developmental, biological and environmental factors, it is necessary to address this disease with an integrated and comprehensive treatment strategy (Son, Kim, 2020). Several drugs have already been developed for its treatment and control. Anti-obesity drugs have different mechanisms of action, such as neural inhibition of appetite and inhibition of fat absorption by the digestive system (Kajimura, Saito, 2014). However, these drugs have a number of contraindications and undesirable side effects, impairing adherence to treatment and, consequently, its effectiveness (De Ferranti, Mozaffarian, 2008; Kajimura, Saito, 2014). Therefore, even with different drugs available, hypocaloric diet and increased physical activity, disease obesity management is not always possible (De Ferranti, Mozaffarian, 2008). In addition, the constant dissatisfaction with body shape influenced by sociocultural pressure has reached unprecedent levels. Thereby, many individuals give up safe nutritional and pharmacological treatment to seek fast and unconventional weight loss methods in search of the perfect body (Sousa et al., 2020).

2,4-Dinitrophenol (2,4-DNP or DNP) is a drug known to cause rapid weight loss, but it is associated with a high rate of danger-

ous adverse effects. The drug acts as a thermogenic, inducing the uncoupling of oxidative phosphorylation in mitochondria which results in increased basal metabolic rate and dissipation of energy stored in adipocytes in the form of heat (Grundlingh et al., 2011). Several studies currently describe the activation of thermogenesis as a possible therapy to aid in the weight loss of obese individuals, as well as the use of drugs with thermogenic action (Wang et al., 2021). However, the use of DNP presents a high risk of toxicity even in small doses, which can cause the death of the individual (Grundlingh et al., 2011; Sousa et al., 2020). The sale and use of this drug are prohibited in several countries, including Brazil, due to the great risk to health it represents (Brazil's Ministry of Health, 2020). However, DNP is still sold clandestinely on the internet, under different names and in the form of supplements, as a promise of fast and safe weight loss (Sousa et al., 2020). Several fatalities related to exposure to DNP have been reported in recent decades and in many cases, weight loss was the desired goal (Sousa et al., 2020).

Despite the relevant health risks that its use presents, information about DNP, its mechanism of action and toxicity are still scarce in the literature. Mostly, information about the effects promoted by DNP derives mainly from reports of intoxication cases reported in emergency care units (Sousa et al., 2020). Once the individual presents intoxication after consumption or exposure to the drug, there is no antidote or specific treatment that helps in his recovery. Still, despite the danger, the consumption of DNP has been increasing in the community of bodybuilders and people who practice crash diets, mainly teenagers and young adults (Bleasdale, Thrower, Petróczi, 2018). In this context, this article aims to provide an updated review of information about DNP and its use as a weight loss agent, which can contribute to the dissemination of knowledge and awareness of the risks of its use.

3. Methodology

Initially, a review of information in the literature about the DNP and its historical context in society was carried out. Subsequently, to evaluate reports of toxicity cases caused by the use of DNP as a weight loss agent, a literature review was carried out using online search tools in three different electronic databases: Scientific Electronic Library Online (SciELO), National Library of Medicine (MEDLINE) and Google Scholar. The keywords used in the research were: (i) 2,4-DNP; (ii) 2,4-DNP effects; (iii) 2,4-DNP obesity; (iv) 2,4-DNP weight loss; (v) 2,4-DNP toxicity. Thirteen articles containing case reports, dating from 2000 to 2022, were included. Works containing: (a) described the use of DNP as a chemical; (b) case reports of the use of DNP for purposes other than weight loss and c) intoxication due to accidental exposure to the product were excluded (Figure 1). The articles were selected and evaluated by the authors of the present study in consensus. The selection was performed primarily through the titles and abstracts and once selected, the full reading and analysis of the article data was performed. During this selection, 56 articles were found, with 13 works included at the end.

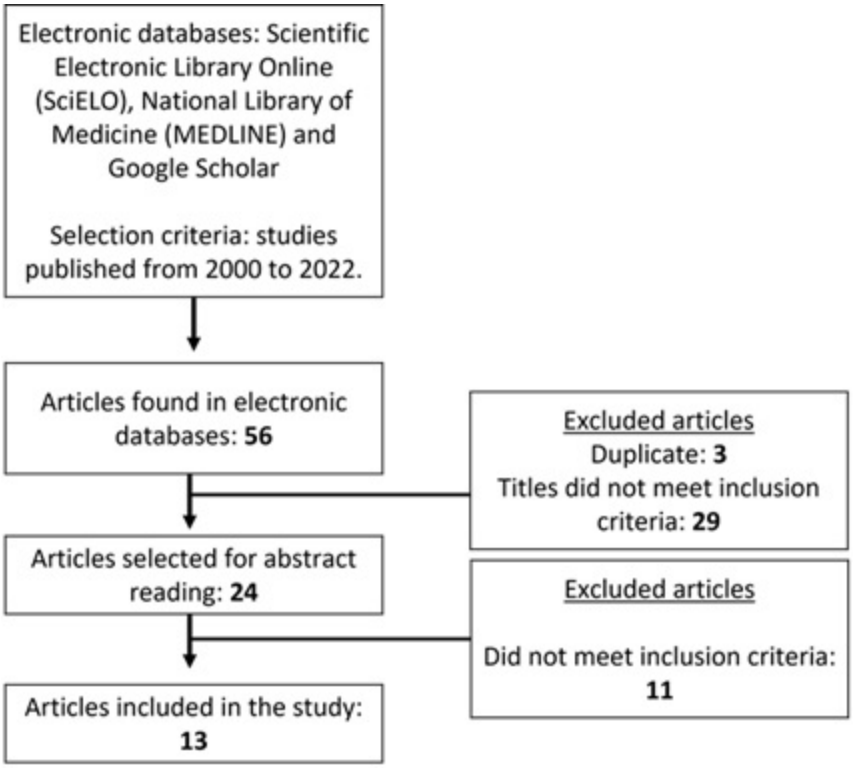

Figure 1: Selection of articles containing case reports of the risks associated with the use of DNP to lose weight.

4. 2,4- Dinitrophenol (DNP): Historical Background

DNP has been used as an industrial chemical for several decades, with several commercial applications, including the manufacture of ammunition and explosives, dyes, pesticides, preservatives and even for developing photographs (Newport, Said, 2020). Before reports about its ingestion, cases of poisoning by occupational exposure by DNP had already been described: the oldest occurred in the First World War, between 1914-1918, in a group of French workers who produced explosives using the compound, being the first DNP exposure-related death reported in 1918 (Perkins, 1919; Warthin, 1918). Interestingly, in addition to symptoms such as high fever, sweating, nausea, diarrhea and vomiting, workers exposed to DNP had a distinct symptom in common: weight loss (Siegmueller, Narasimhaiah, 2010).

In 1933, after carrying out studies on animals, Maurice Tainter, a researcher at Stanford University (USA), observed that the ingestion of DNP also caused marked weight loss in humans by increasing the metabolic rate by up to 50% (Tainter, Stockton, Cutting, 1933). As a result of this research, the drug soon became popular and was available to the population without a prescription. This popularity was boosted by several scientific publications that ensured that the drug promoted weight loss quickly and safely (Cutting, Mehrtens, Tainter, 1933; Newport, Said, 2020; Tainter, Stockton, Cutting, 1933). Despite claims that the drug would be safe to use, the US Board of Pharmacy and Chemistry (1933) issued warnings about the potential toxicity of the drug, while it was widely publicized to the population (Bleasdale, Thrower, Petróczi, 2018).

At a scientific meeting in 1934, Tainter provided a study attesting to the safety of using DNP after treatment of 113 obese subjects. At the same time, it is estimated that at least 100,000 Americans had already used the drug. Despite this, in that same study, the researcher reports that only three fatalities, two due to hyperpyrexia, came to light. According to the author, deaths occurred after ingestion of high doses of the drug (Tainter, Stockton, Cutting, 1934). In 1935, Tainter et al. published another study where he reported the treatment of approximately 170 obese patients with dinitrophenol for an average of 3 months. In this study, the authors demonstrate that using an average daily dose of 300 mg, monitored patients lost about 1.5 lb (680 g) per week, with the presence of some adverse effects considered by the researchers to be of no concern (Tainter, Stockton, Cutting, 1935). In this context, Tainter and colleagues concluded that DNP was an effective and safe way to induce weight loss in obese individuals and that related negative reactions could be avoided by limiting the dose or discontinuing the drug (Tainter, Stockton, Cutting, 1935).

At the time, although Tainter's studies claimed the efficiency and apparent safety of using DNP, other researchers disagreed with his findings (Colman, 2007). Some studies questioned whether the drug was really efficient as a medication for the treatment of obesity (Strang, Evans, 1935), while other studies questioned its safety, as they observed several important side effects, such as hyperthermia, tachycardia, diaphoresis, cataract, liver failure and agranulocytosis (MacBryde, Taussig, 1935; Jung et al., 2020). Still in 1935, the Council of Pharmacy and Chemistry of the United States of America (USA) issues a new warning, considering the use of DNP for the treatment of obesity unacceptable, due to its serious side effects.

DNP was then used in the form of diet pills for the treatment of obesity between the years 1933 and 1938 under the brands Dinitriso, Nitromet, Dinitrenal, and Alpha Dinitrophenol. In 1938, after numerous evidence and reports of serious side effects, it was officially recognized that DNP had potentially lethal adverse effects and posed a threat to public health, which resulted in the immediate withdrawal of diet pills from circulation, just five years after their introduction. in the pharmaceutical market (Bleasdale, Thrower, Petróczi, 2018; Grundlingh et al., 2011). In the same year, the drug was banned by the Federal Food and Drug Administration (FDA) (FDA, 1938). Its use as a chemical was largely withdrawn from commercial use in the 1980s due to reports of the drug's teratogenic potential (Duflou, 2019).

In the 1980s, the use of DNP as a weight-loss agent started to grow again, resulting in new reports of poisoning cases from ingestion of the compound, in addition to a death in a private weight-loss clinic in the USA (Grundlingh et al., 2011). It was only in 2003 that the Food Standards Agency (FSA), the agency responsible for food safety in the United Kingdom, banned the use of DNP as a weight loss agent. In 2015, an alert was issued by Interpol in collaboration with the World Anti-Doping Agency, reinforcing the risks associated with the use of this compound (INTERPOL, 2015; Sousa et al., 2020). Despite the efforts of regulatory bodies to prevent access to the DNP, the ease of access and availability on the internet makes this work difficult, causing the population to still be able to use the drug (Bleasdale, Thrower, Petróczi, 2018).

5. Pharmacokinetics of DNP

2,4-DNP is an isomer of synthetic origin, with molecular formula C6H4N2O5, belonging to the family of dinitrophenols, compounds known for their high toxicity (Figure 1A) (Lu, Jiang, Huang, 2011; Sousa et al., 2020). It has the appearance of a yellow crystalline solid, with a mold-like odor and is poorly soluble in water, as it is a lipophilic compound (Figure 1B) (Lu, Jiang, Huang, 2011). DNP is rapidly absorbed from the gastrointestinal tract, respiratory tract and even through intact skin. Its lipophilicity and low molecular weight allow DNP to be rapidly absorbed by passive diffusion, where the drug then binds to plasma proteins and is distributed to different organs and tissues, such as the liver, kidneys and eyes (Janz, 2014; Sousa et al., 2020).

DNP is mainly metabolized by the reduction of nitro groups through the action of microsomal and cytosolic nitroreductases,

using nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor. Therefore, the human organism is able to slowly transform part of 2,4-DNP into its metabolites 2-amino-4-nitrophenol, 2-nitro-4-aminophenol and 2,4-diaminophenol and their glucuronic acid conjugates, which have less toxicity than the original compound (Janz, 2014; Sousa et al., 2020).

Metabolites and unchanged DNP itself are preferentially eliminated via the urine, approximately 3-4 days after exposure if the kidneys and liver are functional. In case of impaired renal and hepatic function, the elimination of these compounds from the body may be slower, worsening the prognosis of the individual who is actively intoxicated (Sousa et al., 2020). The half-life of DNP in humans has been verified in different studies and their results are still conflicting, being currently estimated between 5 and 14 days (Janz, 2014; Sousa et al., 2020).

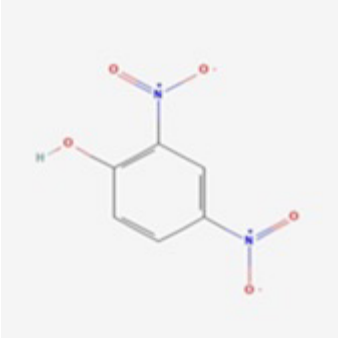

Figure 1: (A) Structure of the 2,4-Dinitrophenol (DNP) compound. (PUBCHEM, 2022).

6. Mechanism of Action and Toxicity

In 1948, researchers Loomis and Lipmann discovered the mechanism of action of DNP: regardless of its route of entry into the body, the substance acts as a protonophore, that is, it has the ability to displace protons through lipid bilayers. In this way, DNP acts as one of the most potent uncouplers of mitochondrial oxidative phosphorylation ever known, resulting in rapid energy consumption that is dissipated in the form of heat, without the production of adenosine triphosphate (ATP). This process is called tremor-independent thermogenesis. To supply the energy deficit caused by this mechanism, fat metabolism is increased, leading to an increase in basal metabolic rate and consequently weight loss (Le, Wood, Kumarasinghe, 2015).

Mammals naturally have an uncoupling protein located in the inner membrane of mitochondria of brown and beige adipose tissue, called thermogenin or UCP1 (Uncoupling protein 1). This protein has the function of generating heat and maintaining the body temperature of these organisms (Goldgof et al., 2014). However, both the need and the ability of this tissue to generate heat is much greater in small mammals, such as rodents, than in adult humans, who have considerably smaller deposits of brown adipose tissue in their body (Ravussin, Galgani, 2011).

In the last decades, in vitro and in vivo studies have shown that the activation or recruitment of brown and beige adipose tissue promotes an increase in the efficiency of metabolism and energy expenditure of the organism, a decrease in adiposity and an increase in glucose tolerance, thus being a target. therapy relevant to the treatment of obesity and its comorbidities (Hanssen et al., 2016; Poher et al., 2015; Vijgen et al., 2011; Vijgen et al., 2012). Therefore, the use of a chemical uncoupler that is presumably active in all tissues could be a complementary approach to the pharmacotherapy of obesity in humans (Goldgof et al., 2014).

However, the margin between beneficial and toxic effects caused by chemical uncoupling of DNP is extremely small. Therefore, in many cases the misuse of DNP can lead to the development of generalized toxicity, mainly through the exacerbated production of heat, which causes a failure in thermoregulatory homeostasis, which consequently results in uncontrolled hyperthermia. Hyperthermia is one of the main deleterious effects observed in individuals who use the drug (Grundlingh et al., 2011). Furthermore, the increased metabolism caused by the use of DNP can cause profuse sweating, notable hyperpyrexia and hyperlipidemia (Lu, Jiang, Huang, 2011). Other mechanisms are involved in DNP toxicity, such as: (i) stimulation of glycolysis, resulting in increased production and accumulation of lactic acid; (ii) accumulation of potassium and inorganic phosphate in the body; (iii) teratogenesis, mutagenesis and carcinogenesis; (iv) liver injury and neutropenia, related to its direct toxic effects or DNP-induced systemic inflammatory response syndrome (Lu, Jiang, Huang, 2011; Grundlingh et al., 2011).

7. DNP as a Weight Loss Agent: Effects on the Body and Intoxications

In the last two decades, the use of DNP as a weight loss agent has become popular again among young adults and bodybuilders who want to lose weight and obtain results faster. This return was possible thanks to the increasing availability and marketing of this banned substance on the Internet (Le, Wood, Kumarasinghe, 2015). However, with the increase in its use, there was also an increase in reports of intoxications and deaths related to the ingestion of DNP with the aim of losing weight (Sousa et al., 2020).

The classic symptoms observed after overdose of phenol-based products, as in the case of DNP, is a combination of hyperthermia (and secondary symptoms related to an exacerbated and uncontrolled increase in body temperature), tachycardia, diaphoresis and tachypnea (Grundlingh et al., 2011). However, symptoms can progress to profound hyperthermia, methemoglobinemia, seizures, coma, muscle stiffness, rhabdomyolysis, multiple organ failure, cardiopulmonary arrest, and even death.

To date, no guidelines are available for the treatment of DNP poisoning. Treatment should be performed symptomatically, in order to control the clinical manifestations by the patient (Sousa et al., 2020). Some strategies for controlling intoxication are described in the literature, such as:

• the use of activated charcoal to reduce the absorption of DNP by the body;

• cooling the body through cold baths, administration of benzodiazepines or dantrolene (still under study);

• restoration and perfusion support including replacement of insensible fluid losses due to fever and diaphoresis;

• maintenance of the airways to avoid respiratory compromise;

• treatment of complications such as seizures, hypotension and methemoglobinemia;

• administration of benzodiazepines to treat anxiety and agitation (Grundlingh et al., 2011; Hsiao et al., 2005; Newport, Said, 2020; Sousa et al., 2020).

To assess the harmful effects of using DNP as a weight loss agent, a selection of case reports was performed, as described above. The information evaluated in these works is summarized in Table 1.

Table 1: Case reports of poisoning by DNP used as a weight loss agent.

Autor/Year of Publication	Age/Gender	Simptoms	Clinical outcomes
McFee *et al*., 2004	22 years old / male	Diaphoresis, fever, agitation, delirium, bradycardia.	Pacient died.
Hsiao *et al*., 2005	17 years old / female	Fever, tachycardia, agitation, confusion, cramps.	Pacient died.
Miranda *et al*., 2006	17 years old / female	Fatigue, tiredness, myalgia, nausea, vomiting, diaphoresis, tachypnea, lethargy, hypotension, respiratory arrest.	Pacient died.
Tewari *et al*., 2009	27 years old / female	Fatigue, nausea, diaphoresis, tachycardia, fever, agitation.	Pacient died.
Le; Wood; Kumarasingh, 2015	21 years old / male	Fever, headache, skin irritation, swelling of body parts.	Patient recovered within a few days.
Holborow *et al*., 2016	21 years old / male	Tachycardia, tachypnea, tiredness, fever, hypertension.	Pacient died.
Zack *et al*., 2016	50 years old / male	Nausea, vomiting, diaphoresis, tachycardia, tachypnea.	Pacient died.
Perez, Gale, Abe, 2017	18 years old / male	Shortness of breath, palpitations, dizziness, nausea, vomiting, lethargy, tachycardia, hypotension, fever, agitation, diaphoresis, skin discoloration, cardiac arrest.	Pacient died.
Patankar *et al*., 2020	22 years old / female	Fatigue, diaphoresis, myalgia, vomiting, tachycardia.	Pacient died.
Sarwar *et al*., 2020	25 years old / male	Palpitation, diaphoresis, nausea, vomiting, shortness of breath, agitation, tachycardia, mild tachypnea.	Pacient died.
Jung *et al*., 2020	39 years old / male	Found dead after ingesting DNP to treat obesity.	Pacient died.
Freeman *et al*., 2021	23 years old / male	Trauma patient required emergency surgery but suffered rapid deterioration under anesthesia due to DNP consumption.	Pacient died.
Griffiths *et al*., 2021	23 years old / male	Diaphoresis, fever, tachycardia, hypertension, agitation.	Pacient died.

8. Discussion

Thirteen case reports of individuals intoxicated after using DNP as a supplement or weight loss medication were evaluated. It is observed that most of them are young individuals, with an average age of 25 years old. In recent decades, there has been a considerable increase in the overweight and obese population worldwide. This fact, related to social pressure driven by the media and social networks to lose weight, has resulted in the increase in popularity of drugs that promise to promote rapid weight loss, especially by young adults (Derenne, Beresin, 2017; Bleasdale; Thrower; Petróczi, 2018). Another relevant data observed is in the gender of the individuals who suffered intoxication: most of them are men. Germain and colleagues in 2021 investigated why the majority of DNP users were men. As a result, they showed that DNP is a drug widely used by sports practitioners and bodybuilders, an environment still very controlled by men. Furthermore, in this study it was seen that female use of DNP is often stigmatized because the potential risks are seen as at odds with women's roles as mothers and caregivers. These findings perhaps partially explain the data seen here.

Evaluated patients demonstrated a wide range of symptoms after ingesting DNP; however, the main signs observed were fever, dia-

phoresis, tachycardia and agitation. In addition, it is also observed that only 1 patient among the reported cases recovered from intoxication, which demonstrates a mortality rate of approximately 91% of the individuals evaluated in the studies in question. Grundligh et al. in 2011, reviewed several cases of overdose from DNP ingestion and observed that patients sought help on average after 7-8 hours after ingestion, with death after approximately 14 hours on average. Therefore, it is possible to observe a rapid evolution of symptoms and deterioration of the clinical case, which in most cases cannot be reversed.

9. Concluding Remarks

In this context, it is possible to conclude that clinical studies are needed to evaluate treatments for cases of intoxication by ingestion of DNP. In addition, these data together reveal the need to implement strict measures to prevent the illegal sale of this prohibited drug over the internet, in addition to the dissemination of the fatal consequences of DNP, to alert the target audience about the dangers associated not only with DNP but other unregulated weight loss drugs.

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