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# Therapeutic drug, toxic drug, and narcotic drug; the fascinating story of the same chemical molecule having three 'faces'.

# Therapeutic drug, toxic drug, and narcotic drug; the fascinating story of the same chemical molecule having three 'faces'.

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## Abstract

Alcohol and drug addiction is causing serious social, as well as personal, problems. At the same time, many substances causing addiction have over time also been shown to have important therapeutic effects. For example, morphine has a long standing place in medicine as an outstanding pain reliever. In addition, a number of other substances, being classified as narcotics (i.e. causing addiction), are currently the target of a renewed interest and investigated for their putative ability to have therapeutic effects in some medical conditions where subpopulations of individuals show treatment resistance to standard medication/treatment. In an effort to shed further light on these issues, the present paper aims to clarify the basic concepts of toxicology, pharmacology, the human nervous system, as well as physiological mechanisms behind addiction.

Key words: *toxicology, pharmacology, human nervous system, addiction, morphine, ketamine, pain, depression*

## Background

In the early 1600$^{th}$ century a man named Paracelsus, the son of a physician, with special interest in chemistry and biology and an expert in occupational medicine, correctly stated that ”All substances are poisonous, there is none that is not a poison. The right dose differenciates a poison from a remedy” (see e.g. Deichmann et al., 1986). Another way of putting it could be that 'there are no safe chemicals only safe ways of using them'.

So what does this really mean? The concept of compounds being used for treatment of human diseases dates back to at least 1500 BC. Substances used were mainly found in different parts of plants (roots, leafs, seeds etc) and mushrooms, but also in animals, such as for example snake toxins. The effects of many substances on human biology were first discovered from a toxic perspective. In the ancient Greece and Roman societies for example there was an obsession with finding poisonous substances to be used as a way of getting rid of political enemies or as punishment for criminal behavior. This was an indicator of the, later discovered, fact that a common denominator for all biologically/physiologically active substances (from medicinal plants to synthetically developed drugs) is their ability to be both therapeutic and toxic. This is also the

basis for our current concept of drug therapeutic effects versus its unwanted side effects (i.e. its toxicity).

Part of early 'drug discovery' was the search for substances with stimulating effects on the central nervous system. Although this mechanism of action was not yet known at the time. Effects were only observed. Many of these substances (such as caffeine, cocaine, alcohol; but also cannabis, mescaline, psilocybin) have retained status as an important part of our society, sometimes called recreational drugs. Other substances, that were early discovered for their biological activity, are for example the cholinergic compound atropine, morphine/opium (a potent pain reliever), the plant extract digitalis (used in cardiovascular disease; although less so in recent years), the noradrenergic acting ephedrine, as well as cannabis, currently much debated. In similarity with atropine, many neuromuscular toxins, used for example in biochemical warfare, as well as drugs used for medical purposes, act on the autonomic nervous system and on skeletal muscles via the neurotransmitter acetylcholine.

The overall point being that many chemical molecules (as listed above) have both the ability to heal and to harm. In addition, many of those having stimulating effects on the central nervous system are also able to cause dependence/addiction as they tend to produce states of pleasant, euphoric and/or calming feelings. In those cases we are dealing with chemicals that, in addition to being therapeutic and toxic (depending on dose), are also narcotic.

## The concept of toxicology

Toxicology is usually defined as 'the study of the harmful interactions between chemicals and biological systems' (see suggested readings in list of references). Along with an increasing awareness of the problems with toxic substances in our environment and how we can prevent them from polluting our environment, focus has the last decades increased on research investigating the mechanisms of toxic compounds/chemicals and their effects on human beings, animals and plants. This article, though, will focus on chemicals interfering with human physiology only. These chemicals range from inorganic chemicals to organic molecules. As indicated above, most of the chemicals have properties that in some settings are toxic, while in other settings may work therapeutically or at least not causing toxic effects. How is that possible? A poison is a poison, right? No, unfortunately it is not that simple. A number of factors are decisive in this 'game'. These factors are: **dose, exposure** – how often, and duration – over how long **time** (timeframe) have you been exposed (Table 1). In addition, depending on their mechanism of action, you need to take into account how a chemical gets into and out of your body and in which form it is able to enter/be absorbed by your body. For example, some chemicals can emit gases that enter your body by inhalation, some can cross your skin barrier and enter your bloodstream just by you touching a surface having a certain amount of the chemical on it. Mostly, however, chemicals get into your body either by ingestion or by (deliberate) injection.

It should be noted here that also your favorite food can be toxic. Currently there is much focus on healthy eating, healthy lifestyle, a healthy mind etc. This is of course good, but it is important to go back and remember the important factors: dose, exposure, how long (time). Food that is considered healthy (or bad) all consist of a number of chemicals (some natural, some added) that may be healthy in a certain dose range and in a certain amount. However, if you overdose and/or eat a lot (maybe also over a long time) you may end up getting levels of the chemical in your body that will have toxic effects. Those could appear more or less immediately, but could also appear first after long time use.

**Table 1**

**Pharm/tox concepts – dose – how often – how long - risk**

| | | | |
|---|---|---|---|
| **Dose:** | **low** | **medium** | **high** |
| **Frequency:** | **rarely** | **weekly** | **daily** |
| **Duration:** | **1 year** | **years** | **decades** |
| **Risk zone:** | **Blue** | **green** | **red** |

So what about a healthy life style or even a healthy mind? That sounds great doesn't it? Couldn't be any toxic risks there? Yes there could be, and I am not kidding. Everything we do often, and maybe pushing towards the extreme, will affect our body and physiology – dose, exposure, time. So think twice before you take on a special concept of life style/diet or concept of working on your mindset. There are currently a number of concepts in these areas offered as business packages to improve your well-being. Listen to your body and your common sense, and read up on the facts.

To wrap up, let us go back to what was stated in the introduction above, 'many chemical molecules have both the ability to heal and to harm. In addition, many of those having stimulating effects on the central nervous system are also able to cause dependence/addiction', and become a little more specific by giving an example. Morphine (belonging to a group of drugs named opiates) is a well known and excellent example of a substance holding the ability to heal/be therapeutic/do good and to harm, and is also able to cause dependence/addiction (i.e. it is also considered narcotic). From a toxicology point of view, the most dangerous toxic property of morphine is its ability to cause decreased respiration that can be deadly.

Morphine will be used as an example throughout the present paper.

## The concept of pharmacology

The concept of pharmacology basically overlaps with toxicology. Only pharmacology is typically more tied to therapeutic thinking, medication and drug development. General pharmacology deals with how substances get into your body, how they can be transported to various parts of your body, how long a certain amount of substance will stay in your body, and finally how it is broken down and eliminated from your body (i.e. administration/ absorption, distribution, metabolism, elimination, ADME) (see Rang & Dale's Pharmacology, in suggested readings below). This is called pharmacokinetics. When finding out if a certain molecule could be used in the treatment of a certain disease, you typically use your knowledge about the specific ADME/pharmacokinetic properties of this molecule. However, you will also need to know what the molecule itself does to the body while inside – its mechanism of action or pharmacodynamics (see Rang & Dale's Pharmacology, in suggested readings below). Simply put, depending on the symptoms of the disease, you may want to look for molecules with properties that either speed up or slow down or to some extent are blocking physiological events. Going back to **morphine,** from a pharmacological and medical aspect most people know that morphine is a potent pain reliever/analgesic. It is used in hospital surgery settings, but is also available as pills (taken orally) for the treatment of various medical conditions that are causing pain. It does this by preventing pain signals from going to the

brain and thus making you aware of the pain. The mechanism of action of morphine molecules to prevent pain experience is by stimulating the opioid 'system'. And so, although morphine can be deadly (as pointed out above), morphine can also be used therapeutically and has a crucial and important place in the control and treatment of pain. The matter of **dose given** should also be stressed here as an important factor for morphine being either therapeutic or toxic.

## The human nervous system and some physiological aspects

The human nervous system includes the brain and the spinal cord (the central nervous system; CNS) as well as projections from CNS to different parts of our bodies (the peripheral nervous system; PNS). In addition, there is the autonomic nervous system that is running the activity of many of our inner organs (such as for example cardiovascular events) (https://en.wikipedia.org/wiki/Nervous_system; suggested readings). This part of the nervous system is called autonomic because it runs many physiological events without us needing to take an active part in these events. That is, you don't need to actively think about the heart beating or your intestines digesting your food.

Populations of various cells belonging to the nervous systems communicate with each other and with cells in body organs by a combination of electric impulses and a subsequent release of biochemicals. Tissue mediating this communication between cells are called receptors. These receptors typically are relatively large protein molecules located either in the cell membranes, inside the cell or existing as circulating targets. Common endogenous biochemicals active in physiological events of the CNS and PNS are dopamine, serotonin, acetylcholine, noradrenaline/adrenaline, together with mediators such as the excitatory glutamate and the inhibitory GABA (gamma-amino-butyric-acid). In addition, it turns out that our nervous system also has an opioid 'system' with its own opioid receptors (used by for example morphine), as well as a cannabinoid 'system' with its own cannabinoid receptors (used by for example cannabis, that also gave the 'system' its name). In the present paper, focus will be on the dopamine system (involved in drug dependence/addiction and the so called reward system), but other systems listed above will also be part of the discussion when relevant.

## The concept of drug dependence/addiction

How come you get addicted to something in the first place? You are in control of your body right? No, wrong. Your brain has the overriding control and power over: i) what goes on in your body and ii) how you behave.

All substances (and activities) that can cause addiction/dependence work by stimulating the brain dopamine mesolimbic pathway – causing increased dopamine release in the brain ventral striatum (”the reward system”) (Fig. 1). Compulsive self administration can be observed also in laboratory rats, indicating that addiction can occur also in animals. In addition, instant/rapid effect following intake is crucial. Therefore way of administration is important: such as for example intravenous – snorting – patch.

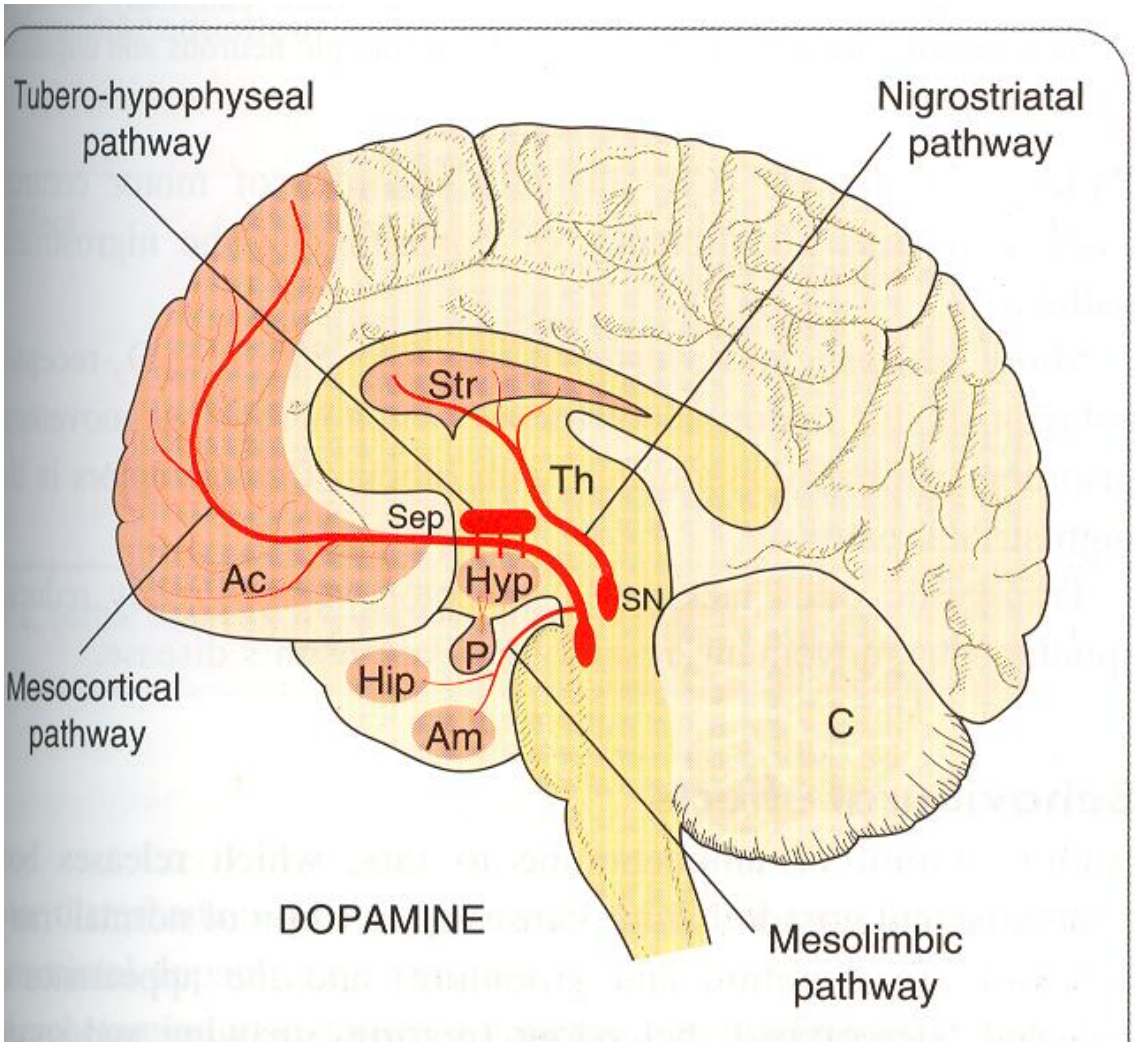


***Figure 1****. The figure shows a schematic drawing of the brain dopaminergic pathways with special focus on the mesolimbic pathway. Adapted from Rang & Dale's Pharmacology*

So when do you know that someone is truly addicted? What are the criteria? The Diagnostic and Statistical Manual of Mental Disorders (DSM; Fig. 2) states the criteria for addiction to be: i) substance taken in larger amounts or over a longer time period than intended; ii) desire and unsuccessful efforts to control/cut use; iii) great deal of time spent on activities obtaining substance; iv) social, occupational activities as well as relations are reduced or neglected in favor of substance obtaining and use; v) continued substance use despite knowledge of health risks.

Use starts very much like a romance with a destructive personality partner – first total euphoria – then a slippery slope to total disaster. You keep on using the drug and increasing the dose hoping for the moments of true euphoria first experienced, that, however, are gradually occurring less and less often. This is mostly due to a tolerance development in brain tissue involved in the mediation of the euphoric effects. Abstinence is clear and present, terrible and in some cases truly dangerous. In summary, addiction comes with initial euphoria, tolerance development causing the need to up the dosing, abstinence/withdrawal, loss of control, and desire to stop using the drug.

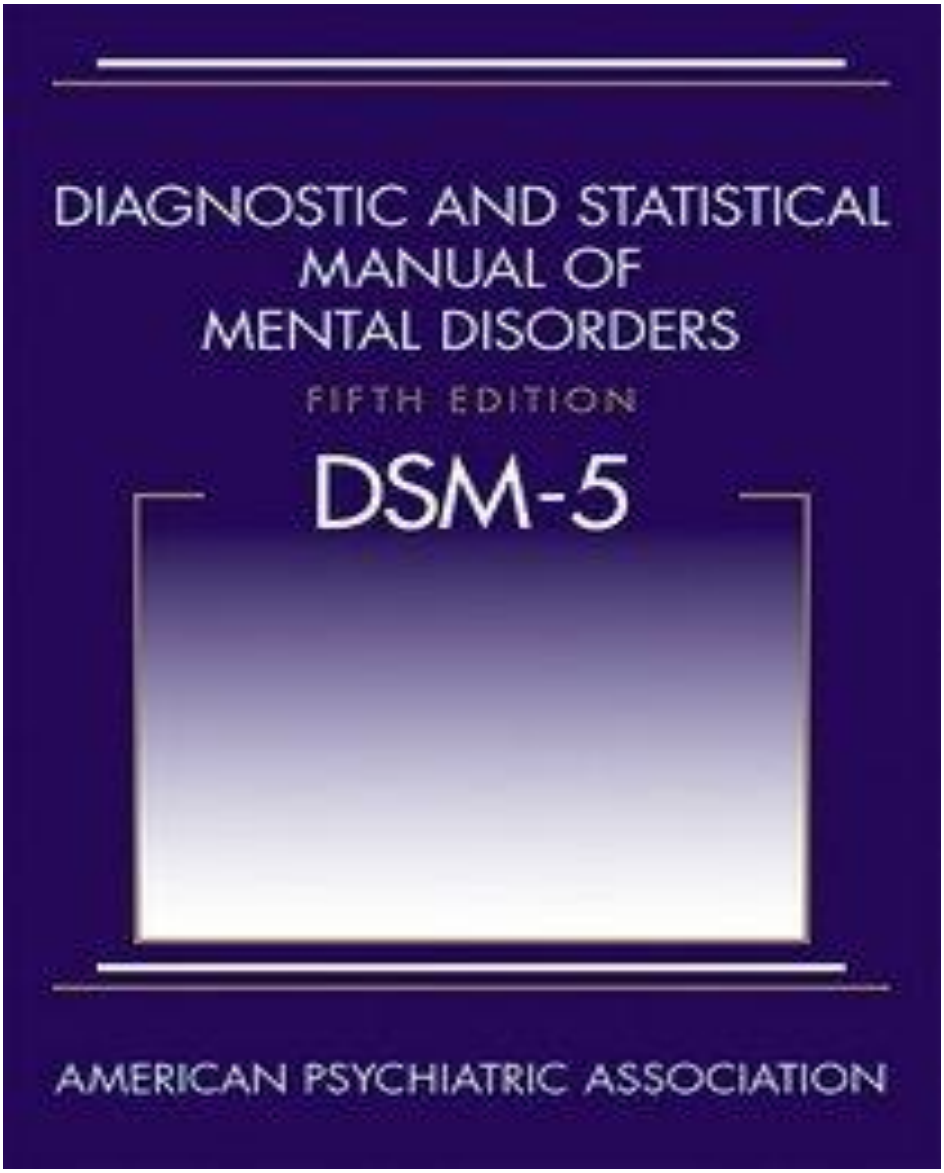


***Figure 2**. The Diagnostic and Statistical Manual of Mental Disorders*

## Who gets addicted – various reasons

There are some genetic markers as to different individuals' physiology make-up handling for example alcohol differently (tolerance, breakdown/elimination etc). Also, individuals with specific personality profiles are suggested as being particularly vulnerable. But currently there is a consensus to stay away from that concept of thinking, in part due to the scientific evidence being somewhat weak.

Other explanations have been: i) childhood trauma; ii) low self esteem; iii) efforts to self-medicate (for example in certain psychiatric conditions); iv) some individuals being genetically low in dopamine and/or serotonin causing special needs for stimulation to feel good.

At this point, back to our example morphine. As stated above, morphine belongs to a group of drugs named opiates that are categorized as narcotic substances. Included here are: heroin, morphine (a heroin active metabolite), opium, and codeine. Also note that in the nervous system there is an endogenous morphine called endorphine having similar properties and effects as

morphine. We noted above that morphine decreases respiration. Decreased respiration is often the cause of death due to OD (over dose) among heroin users. Heroin is broken down/metabolized to form morphine when administered.

And so now we are coming full circle with the example of morphine: this is a drug (coming from plants – opium poppy) that is used therapeutically as a pain reliever/analgesic; that is so toxic that it can be deadly (decreased respiration; from a toxicity aspect this is considered a serious side effect; another serious side effect is adrenal gland disturbance); and is highly addictive, mostly in the form of heroin (injected intravenously), and therefore categorized as a narcotic drug. Again, these properties are dose, exposure, time related.

So are there other drug molecules having the same property profile as morphine? That is, being both therapeutic, toxic and narcotic in a dose- exposure-time dependent way? Yes there are – quite a few in fact. Amphetamine/methylphenidate for narcolepsy and ADHD; cocaine – local anaesthetic; ketamine – anesthesia, pain relief, also currently investigated for treatment of depression (see e.g. Zarate et al., 2006; Tiger et al., 2020); cannabis – pain relief, tranquillizer (García-Gutiérrez et al., 2020); LSD, psilocybin (see e.g. Gregorio et al., 2021), MDMA – for post-traumatic stress disorder (PTSD) (Feduccia and Mithoefer, 2018), and ibogain (Cameron et al., 2021). Many of these molecules were studied for potential therapeutic effects already in the 1950's. However, the hippie movement (in the mid-1960's) with its gloryfying message about the use of these drugs caused the passing of prohibitions of the use and selling of these drugs due to concerns about their toxic property profiles. This in turn also put an end to research on these drugs for potential therapeutic properties. Currently, though, there has been a renewed interest in resuming this kind of research (see references above), since there is evidence to believe that some of these drugs can indeed be of therapeutic value for some subpopulations of patients that do not respond effectively to standard medication. The idea being that some of these molecules could be chemically modified to decrease toxic/narcotic liability but with retained therapeutic effect.

## Concluding remarks

So, where am I going with this? What is the take home message? My main point here is that in many cases there is a fine balance between the important therapeutic effects of a number of substances, their toxicity (in the form of serious side effects), and their propensity to cause dependence/addiction. The question then is: are we going to avoid using these drugs that have been shown to have excellent, and sometimes unique therapeutic effects just because we are afraid of the side effects and the narcotic properties? Are we even going to stay away from doing research on these molecules in an effort to tweak the molecule to diminish side effect liability and narcotic properties with retained therapeutic effect, for the same reasons? These are very important questions that need to be discussed openly and open-mindedly. Should narcotic laws and regulations stand in the way of someone not being able to get an effective treatment for their debilitating disease? A certain per cent of individuals (in all societies) do not respond sufficiently well to standard medication for their disease/medical condition (for example states of pain, depression, anxiety). Should we really let them suffer because we are so afraid of using drugs that are labelled narcotics? Would it not be better to be able to do research on how (just as we do with side effect liability) we can use these drugs in a safe way?

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In addition, the present Author would like to refer to the complementary article entitled: 'Chemical modifications of drugs with special emphasis on stereochemistry.' by Ulf Berg, Professor of Organic Chemistry, member of Strömstad Academy.