

# PSYCHOPHARMACOLOGY

The effects of drugs and medication on human brain and behaviour

Leon Kenemans

Third edition

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# Table of contents

<b>Introduction</b>		<b>7</b>
<b>1</b>	<b>What are psychotropic drugs?</b>	<b>9</b>
1.1	Intake	11
1.2	Dosage	12
1.3	Side effects and therapeutic window	13
1.4	Titration and tolerance	14
1.5	Research into how psychotropic drugs work	14
1.6	Placebo-controlled studies	15
1.7	Random sampling and statistics	16
1.8	Pre-clinical and clinical research	18
1.9	Statistical analysis	21
1.10	Conclusion	24
<b>2</b>	<b>The structure of the nervous system</b>	<b>25</b>
2.1	Research methods	25
2.2	The exterior of the brain	26
2.3	Connections to the exterior of the brain	28
2.4	The bottom of the brain	29
2.5	The interior of the brain	31
2.6	Connections with the interior of the brain	33
2.7	Outside of the brain	34
2.8	Autonomic, somatic and peripheral nervous system	37
<b>3</b>	<b>The Neuron</b>	<b>39</b>
3.1	The neuron cell body	39
3.2	The cell nucleus	39
3.3	The genetic determination of behaviour	41
3.4	The function of the nerve cell part 1: the resting state	43
3.5	The function of the nerve cell part 2: from rest to action	46
3.6	The function of the nerve cell part 3: even more action	48
3.7	The function of the nerve cell part 4: even more complicated	49
<b>4</b>	<b>Neurotransmission</b>	<b>51</b>
4.1	The synapse	51

4.2	The availability of neurotransmitters: targets for psychotropic drugs	52
4.3	The postsynaptic processes	55
4.4	Blocking and influencing	57
4.5	Relays	59
4.6	Two forms of neurotransmission	60
4.7	Astrocyte signalling	62
<b>5</b>	<b>Principles of Psychopharmacology</b>	<b>65</b>
5.1	Dose-response curve (DRC)	65
5.2	Potency, efficacy and the therapeutic window	68
5.3	Individual differences in drug response	71
5.4	Non-monotonic DRCs	73
5.5	Receptor interaction	74
5.6	Pharmacodynamics	76
5.7	Pharmacokinetics	78
5.8	Tolerance, sensitisation and desensitisation	81
5.9	Acute versus chronic	83
5.10	In conclusion	85
<b>6</b>	<b>Stimulants</b>	<b>87</b>
6.1	Why are stimulants stimulating?	87
6.2	Caffeine	88
6.3	Nicotine	91
6.4	Amphetamine	95
6.5	Cocaine	97
6.6	Methylphenidate	100
6.7	Other cognitive enhancers (and cognitive enhancers for others)	105
6.8	Costs of (high doses of) stimulants	106
6.9	Methylphenidate versus cocaine: additional remarks	110
6.10	Conclusion	111
<b>7</b>	<b>Mood Stabilizers</b>	<b>113</b>
7.1	Depression and mania	113
7.2	Major depressive disorders and individual differences	114
7.3	Stress and the brain	117
7.4	Chemical imbalance	118
7.5	Antidepressants: the selective inhibition of serotonin reuptake	119
7.6	Other antidepressants	121
7.7	Stimulants and depression	124
7.8	Depression and the immune system	125

7.9	Bipolar disorder: lithium	126
7.10	In conclusion	127
<b>8</b>	<b>Tranquillizers and social enhancers</b>	<b>129</b>
8.1	Avoidance and anxiety disorders	129
8.2	The fear network in the brain	130
8.3	Benzodiazepines	133
8.4	Other anxiety-inhibiting substances	135
8.5	Potential new anxiety inhibitors	136
8.6	Sleeping aids	140
8.7	Social enhancers	141
8.8	Conclusion	143
<b>9</b>	<b>Antipsychotics</b>	<b>145</b>
9.1	Schizophrenia and psychosis	145
9.2	Classic antipsychotics	146
9.3	Aberrant brain circuits: dopamine	148
9.4	Blocking dopamine: side effects	149
9.5	Aberrant brain circuits: other neurotransmitters	150
9.6	Atypical antipsychotics	151
9.7	Sensory protection	153
9.8	In conclusion	154
<b>10</b>	<b>Psychedelics and related substances</b>	<b>155</b>
10.1	General characteristics of psychedelics	155
10.2	Cannabis	156
10.3	The effect of cannabis in the brain	157
10.4	Psychological effects of cannabis	159
10.5	Ecstasy	161
10.6	LSD	162
10.7	Dissociatives and deliriants	165
10.8	Zombie drugs	167
10.9	Therapeutic psychedelics	169
10.10	Conclusion	172
<b>11</b>	<b>Dependence</b>	<b>173</b>
11.1	Desensitisation and tolerance	173
11.2	Liking versus wanting	174
11.3	Quitting smoking	176
11.4	Other addictive substances: heroin	179
11.5	Alcohol	180
11.6	In conclusion	181

<b>12</b>	<b>Neurological disorders</b>	<b>183</b>
12.1	Parkinson's Disease	184
12.2	Huntington's Disease	188
12.3	Alzheimer's Disease	189
12.4	Stroke	191
12.5	Other Neurological Disorders	192
12.6	Epilepsy	194
12.7	Encephalitis: older perspective for a new vista	198
	<b>Epilogue – an opiated summary</b>	<b>201</b>
	<b>Literature</b>	<b>204</b>
	<b>References</b>	<b>231</b>
	<b>Index</b>	<b>232</b>

# Introduction

The purpose of this book is to provide an overview of the manner in which a variety of substances influence the human brain. This is based on the principle that the primary mechanism for influencing behaviour lies in the effects that these substances have on the human brain. These substances are collectively referred to as 'psychotropic drugs', the field of study of the science of psychopharmacology.

The first chapter will primarily deal with the general principles of psychopharmacology: how do psychotropic drugs enter the brain, how can we observe the effects of psychotropic drugs inside the brain, and what kinds of effects do they generally have on the brain? A basic understanding of the structure of the brain and how brain cells function and communicate is essential in the study of psychopharmacology. These topics will be dealt with in Chapters 2, 3 and 4. The subsequent chapters will discuss the specific classes of psychotropic drugs, both those used as medications and those used as recreational drugs. Some chapters will emphasise the characteristics that a group of psychotropic drugs has in common, while others will focus more on the applications, such as those used to treat psychiatric diseases.

## **For the 3rd edition**

Numerous sections have been adjusted to accommodate recent scientific insights. For the same purpose, several new sections have been added. The adjustments and additions include (list not exhaustive):

- Chapter 1: Extensive discussion of relevant statistical principles.
- Chapter 3: New inset on Nernst equilibrium
- Chapter 4: New figure for metabotropic transmission; additional text on generation of EEG oscillations; new section on astrocyte signalling.
- Chapter 5: Additional text/sections on individual differences in dose-response-curves; inverted-U patterns; therapeutic window; therapeutic drug monitoring; tolerance and anticipatory compensatory processes.
- Chapter 6: Additional text on EEG features relevant to ADHD and methylphenidate; use of non-prescribed ADHD medication; comparing methylphenidate to cocaine; chronic fatigue and long Covid.
- Chapter 7: Extensive update on the gene x environment hypothesis for depression; precision psychiatry; new section 7.8 on the role of the immune system; ; new section 7.8 on the role of the immune system.
- Chapter 8: Additional text on stress prevention; new treatments for OCD, GAD; PTSD; hypersensitivity, oxytocin and psychopathy; obesity and impulsiveness.

- Chapter 9: New cholinergic treatments for schizophrenia.
- Chapter 10: New figure for the CB1R feedback loop; new section (10.8) on zombie drugs and (10.9) on recent psychiatric application of psychedelics.
- Chapter 11: Extensive update on the medical and non-medical interventions for smoking cessation.
- Chapter 12: Extensive updates on new treatments for Parkinson's and Alzheimer's disease; extensive new sections on Epilepsy (12.6) and Encephalitis (12.7).

# What are psychotropic drugs?

1

Psychotropic drugs are substances that influence behaviour by affecting the central nervous system, primarily the brain. Some examples include caffeine, alcohol and nicotine, but also sedatives, antidepressants, antipsychotics, and Ritalin. The brain is mostly made up of brain cells, called neurons, which are constantly sending signals to one another. Substances that reach these cells from the bloodstream can influence these signals by causing a chemical reaction with other substances that are already in the brain. These substances already residing in the brain are usually referred to as molecules, proteins or protein complexes, and will be dealt with in a later chapter.

When a psychotropic substance changes a signal somewhere inside the brain, this can have an effect on countless other parts of the brain that are connected to the affected area. Some parts of the brain are in direct contact with the spinal cord, which is in turn connected to muscles, glands and other internal organs. Through the connections between the brain and muscles, a substance can exercise influence on patterns of muscle activity – what we call ‘behaviour’.

## **Inset 1.1: Dart poison**

Tubocurarine is the active ingredient in curare, the dart poison that some South American indigenous tribes use to hunt animals. It has a paralysing effect, because it blocks signals from the nerve pathways from the spinal cord to the muscles. A similar blockage could also occur in the brain, if it were not for the fact that tubocurarine cannot enter the brain from the bloodstream.

But substances can also influence behaviour in other ways, as is the case with tubocurarine (see inset 1.1). Atropine is a substance that has a similar mechanism of action as tubocurarine (what that means exactly will be explained in the following chapters). Its applications include usage of atropine eye drops to dilate the pupil by temporarily paralysing the pupillary muscles, in order to make it easier to examine the inside of the eye. Unlike tubocurarine, atropine can enter the brain from the bloodstream, which results in people reporting side effects such as slurred speech, drowsiness, or confusion. If the amount of atropine administered is not too high, however, it can result in a cheerful and calm sensation, so it is occasionally used for recreational purposes as well.

This brings us to the differences between two categories of psychotropic substances:

recreational drugs and medicinal drugs. People use recreational drugs because the substance has a rewarding effect, similar to that experienced with good food, sex, quenching a serious thirst, or lying down when fatigued. The substance's rewarding effect increases the likelihood that the person will take the drug again when the next opportunity arises. Whether that is one minute later or the next day, depends on factors such as the availability of the substance and the degree of satiation in other parts of the brain or the body. For example, no matter how delicious the meal, at a certain point your stomach is simply full. Many recreational drugs also have a sedative effect: depending on the individual, after a certain amount has been consumed, the sedative effect will be so powerful that the person will not be able to consume any more of the drug. But there are also substances that have a strong rewarding effect, and which generally do not cause the person to feel very satiated. These drugs are more likely to lead to repeated self-administration. We refer to this phenomenon of repeated self-administration as 'addiction'. Examples of addictive substances are nicotine, cocaine and heroin; note that these three drugs have been described as the top three when it comes to addictive potential (Van Amsterdam et al, 2010).

The other category of psychotropic substances is referred to as medicinal drugs or pharmaceuticals. Psychotropic medication is used to reduce, change or otherwise control problematic behaviour. Behaviour is considered to be problematic if it leads to dysfunction in the eyes of the person themselves or those of their surroundings. Some examples of psychotropic medication include sedatives, antidepressants, antipsychotics and Ritalin, as mentioned above.

It should be noted that often a distinction is made between 'psychotropic' and 'psychoactive'. The latter term is then used to refer to substances that influence behaviour by affecting the central nervous system, primarily the brain, e.g., caffeine and alcohol. In contrast, psychotropic drugs would form a subset of psychoactive drugs – specifically those that are used in psychiatry to treat mental disorders, such as sedatives, antidepressants, antipsychotics and Ritalin. As will become apparent however, psychoactive substances may eventually turn out to be useful for treatment (e.g., section 10.9), and psychotropic substances are sometimes applied for recreational purposes (e.g., section 6.6). Therefore, the terms will be used interchangeably throughout the remainder of this text.

There is also a class of pharmaceuticals that mainly suppress inflammation, in the brain, and in other parts of the body. These substances also may have positive psychotropic effects which are especially manifest in a clinical context, in particular for a certain form of depression. This class includes among others pain killers and antibiotics. Their mechanism is mainly based on interactions with the immune system, which is quite different from the mechanism of most substances mentioned above, which more directly influence the signalling between neurons. This will be more extensively discussed in section 7.8.

## 1.1 Intake

The most common way to ingest psychotropic drugs is simply by eating food. This usually involves the proteins in the food, which the body breaks down into amino acids, including the essential amino acids that the body cannot create on its own. These amino acids can then move through the bloodstream into the brain, where they are converted into neurotransmitters, substances that play a crucial role in the transmission of signals between neurons (this is discussed in more detail in Chapter 4). Some examples of neurotransmitters include dopamine and serotonin. The brain produces serotonin from the essential amino acid tryptophan. Products with high concentrations of tryptophan include milk and sesame seeds.

However, when we talk about administering medications and drugs, we generally don't mean eating breakfast. The most common and familiar way to administer drugs is of course via tablets. This is actually a slow and complicated method, however. Before the substance's active ingredient enters the bloodstream, it has to pass through the stomach and other internal organs. The maximum concentration in the blood is only reached after quite some time has passed, and much of the active ingredient is broken down before it reaches the blood. The same applies to administering drugs via food or drink. There are major differences between substances when it comes to the speed with which they can reach a certain concentration in the blood via the stomach. Alcohol, for example, takes around 20 minutes to reach a measurable and subjectively observable concentration in the bloodstream.

Caffeine, the active substance in coffee, takes around twice as long, and a wide range of medications used in psychiatry can take one or several hours.

There is a relation between the course of the concentration of a substance in the bloodstream and the course of the effect that substance has in the brain. At the same time, there are countless other factors that determine the course of the effect in the brain (several of these will be dealt with later in this book). Nevertheless, injecting or infusing a substance directly into the bloodstream is a relatively quick way not only to increase the amount of the substance in the blood, but also to achieve a fast effect in the brain. It is still the preferred method for a wide range of applications, such as heroin use, or initiating the preanesthetic effect that precedes general narcosis. Smoking drugs, such as tobacco, marijuana, cocaine or heroin, is similar to injection or infusion with regard to the speed at which effects occur. The speed of the effects in the brain undoubtedly plays a role in the addictive nature of the substances administered in these ways. Another fast way to increase blood concentration levels is nasal insufflation, or 'snorting' substances via the nose, as is commonly the case with cocaine. Oral intake, such as in the form of nicotine gum, is considerably slower, and intake via the skin, such as in the form of nicotine patches, is extremely slow: maximum blood concentrations are only reached after around five hours. Which factors play a role in the time needed to achieve effects will be dealt with in greater depth in section 5.7 on pharmacokinetics.

There are two ways to 'package' a medication in a tablet. The first method results in the fastest possible increase in blood levels, up to a maximum concentration. That