Self-Experiments with Psychoactive Substances: A Historical Perspective

Torsten Passie and Simon D. Brandt

Contents

T. Passie (✉)
Senckenberg Institute for History and Ethics in Medicine, Goethe-University Frankfurt/Main, Frankfurt, Germany
e-mail: dr.passie@gmx.de

S. D. Brandt
School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK
e-mail: s.brandt@ljmu.ac.uk

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Abstract

The purpose of this chapter is to highlight the rich tradition of self-experiments (SEs) with psychoactive substances carried out by scientists and therapists for more than a century. Scientifically inspired controlled SEs dominated until the end of the twentieth century, when ethical requirements minimized controlled SEs and "wild" SEs expanded particularly with the emergence of new psychoactive substances. The review focuses on laughing gas (nitrous oxide), cannabis, cocaine, hallucinogens, entactogens, and dissociative hallucinogens. This is due to the fact that substances that induce "complex" effects such as alteration of space/time experience, ego dissolution, and increased feelings and insights (e.g., hallucinogens, entactogens) represent by far the majority of SEs, whereas SEs with substances inducing "simple" effects such as euphoria, anxiolysis, dissociation, or emotional blunting (e.g., cocaine, opioids) are much rarer or even absent (e.g., benzodiazepines). Complex drug effects are much harder to describe, thus allowing SEs to fulfill a more important function.

SEs with psychoactive drugs appeared to emerge in the mid-eighteenth century, which triggered a long-standing tradition throughout the nineteenth and early twentieth century. SEs have been de facto performed for a variety of reasons, ranging from establishing scientific knowledge and gaining philosophical insights to compensating for personal deficits. Self-experimenters can be divided into two general types. Besides their scientific intentions, "exploratory" self-experimenters intend to expand awareness and insight, whereas "compensatory" self-experimenters might aim for coping with psychiatric symptoms or personality deficits. Scientific limitations of SEs are obvious when compared to double-blind, randomized, placebo-controlled trials. Whereas the former might lead to more "realistic" detailed description of subjective effects, the latter lead to more solid results in respect to objectively measurable "average" effects. Possible adverse effects of SEs were identified that resulted in loss of scientific objectivity and decreased control over substance use and addiction, development of isolation, problematic group dynamics, and "social autism."

Keywords

Cannabis · Cocaine · Dissociative hallucinogens · Entactogens · Hallucinogens · History of drug use · Nitrous oxide · Psychoactive substances · Self-experiments

Acronyms of the Discussed Psychoactive Substances

2C-B	2-(4-Bromo-2,5-dimethoxyphenyl)ethan-1-amine
2C-E	2-(4-Ethyl-2,5-dimethoxyphenyl)ethan-1-amine
2C-T-2	2-[4-(Ethylsulfanyl)-2,5-dimethoxyphenyl]ethan-1-amine
2C-T-7	2-[2,5-Dimethoxy-4-(propylsulfanyl)phenyl]ethan-1-amine
2C-T-4	2-[2,5-Dimethoxy-4-(propan-2-ylsulfanyl)phenyl]ethan-1-amine
2C-T-21	2-{4-[(2-Fluoroethyl)sulfanyl]-2,5-dimethoxyphenyl}ethan-1-amine
5-HO-DMT	3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-ol
AM-2201	[1-(5-Fluoropentyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone

LSD	(8β)-*N*,*N*-Diethyl-6-methyl-9,10-didehydroergoline-8-carboxamide (d-lysergic acid diethylamide)
MDA	1-(2*H*-1,3-Benzodioxol-5-yl)propan-2-amine
MDE	1-(2*H*-1,3-Benzodioxol-5-yl)-*N*-ethylpropan-2-amine
MDMA	1-(2*H*-1,3-Benzodioxol-5-yl)-*N*-methylpropan-2-amine
MEM	1-(4-Ethoxy-2,5-dimethoxyphenyl)propan-2-amine
MPPP	1-Methyl-4-phenylpiperidin-4-yl propanoate
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

1 Introduction

Since ancient times, it seemed like a usual behavior of humans, and especially so with physicians and scientific researchers, to conduct experiments not only on other humans (volunteers or "paid participants") but also on themselves. From a historical perspective, it seemed appropriate for a long time to conduct experiments on fellow human beings for the purpose of saving lives, for facilitating cure and healing, and/or for providing other benefits. An old principle of medical morality is to never perform an experiment on man if it might turn out to be harmful to any extent.

The ancient Greeks and Romans did not appear to experiment much on healthy or ill people. Hippocrates, the ancient medical philosopher, has even warned doctors to experiment with new and unknown techniques or drugs. This attitude may have contributed to the fact that progress in the medical sciences was put on hold for hundreds of years. Since the medieval ages, medical and other investigators began to experiment on fellow humans and on themselves with the aim of making new discoveries about the human organism and for the purpose of improving treatment options.

The Oxford English Dictionary does not contain the term self-experimentation or auto-experimentation, but it includes the term self-experience. This is traced back to 1778, when it was defined as "those that have self-experience, are usually more affected than those that have things by hear-say only" (Simpson and Weiner 1989).

Self-experiments (SEs) are experiments in which physicians, psychologists, or other researchers serve as their own experimental subjects. The French physiologist Claude Bernard (1813–1878) emphasized the importance of such experimentation: "Morals do not forbid making experiments on one's neighbor or on one's self. . . . Christian morals forbid only one thing, doing ill to one's neighbor. So among the experiments that may be tried on man, those that can only harm are forbidden, and those that may do good are obligatory" (Castiglioni 1947, p. 598).

After World War II, it emerged that such principles were found to be seriously defiled by Nazi doctors in Germany. However, during that time there was no formal code of ethics in medical research to which the judges at the Nuremberg trials could rely on. As a result, the *Nuremberg Code for medical experiments* was established. It was especially found necessary to obtain informed consent from participating subjects for any type of experiment. In respect to self-experimentation, paragraph 5 of this Code includes the following formulation: "No experiment should be

conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians serve as subjects" (Nuremberg Code, quoted in Altman 1986, p. 17). This points toward somewhat lower safety standards with regard to SEs when performed by physicians or other scientists.

2 Self-Experimentation in Medicine

In the eighteenth and nineteenth century, a broader discussion on the issue of self-experimentation emerged. The general opinion prevailed that SEs were considered a requirement before administering any medication to a patient, which was also deemed applicable to other medical procedures such as vaccination or anesthesia. However, not every new medication or treatment was tested in SEs.

The topic of self-experimentation has received little attention in the scientific literature and in discussion surrounding codes of ethics. Altman (1972) found just 137 SEs documented in the medical literature. However, when it comes to SEs with psychoactive substances reviewed here, one has to expand this list significantly. There are more than 100 publications available that involve SEs carried out by medical and psychological researchers, and no bibliography appears to list these SEs.

Reasons for conducting SEs are manifold. Usually, SEs conducted by medical doctors include the following reasons: to observe, to assess therapeutic benefits to accumulate data, to study physiological processes, to explore mechanisms associated with the transfer of infections, to test newly developed instruments (e.g., cardiac catheter), to test instruments or medications for minimizing risks of harm to patients, and/or to explore resilience. In the field of psychoactive substance research, some investigators have repeatedly taken the burden of self-experimentation in an effort to explore the perspective of experimental subjects in order to optimize and refine the procedure and atmosphere needed for appropriate clinical experiments. At the same time, it is recognized that SEs provide only limited data when it comes to modern scientific standards. For example, the inclusion of double-blind, randomized, placebo-controlled trials would be needed to collect solid data on effects and risks associated with psychoactive substances. Nevertheless, in contrast to controlled SEs, more rigorously designed scientific experiments often fail to provide data about the "inner experiences" and more complex subjective effects elicited by psychoactive substances.

Henry K. Beecher, the first professor of anesthesia at Harvard University in Boston, wrote in 1959: "Experimentation upon other men requires a willingness to experiment on oneself as evidence of good faith . . ." (Beecher 1959). A statement made by Sir George Pickering points in the same direction: "The experimenter has one golden rule to guide him as to whether the experiment is justifiable. Is he prepared to submit himself to the procedure? If he is, and if the experiment is actually carried out on him, then it is probably justifiable. If he is not, then the experiment should not be done" (Pickering 1949). These statements imply that the

willingness to SE is a necessary requirement for any experimentation on other human beings. Leo Alexander, who was a major figure in writing the Nuremberg Code, differentiated this point of view: "It is ethically permissible for an experimenter to perform experiments involving significant risks only if the solution, after thorough exploration of all the other lines of … scientific investigation, is not accessible by any other means, and if he considers the solution of the problem important enough to risk his own life along with those of his non-scientific colleagues …" (quoted by Altman 1986, p. 17). However, some significant medical institutions like the National Institute of Health in the USA permit SEs just in those cases where "the same safeguards for the investigator-subject [were provided] as for a normal volunteer." One implication is that all SEs have to undergo a complete medical examination beforehand. The Johns Hopkins Hospital issued a memorandum in 1983, reminding their medical doctors that proposed SEs must be submitted for review in the same way as any investigation using human volunteers (Altman 1986, p. 20).

One prominent example involving SEs was John Scott Haldane (1860–1936). Haldane's experiments were mainly focused on studying the impact of gases on breathing using himself as the main volunteer. His aim was "to achieve knowledge, which could save other men's lives." Haldane argued that experimentation on animals was insufficient because it was conducted on anesthetized animals. Therefore, he started experimenting on himself and a close associate and gained groundbreaking results at the time (Haldane and Smith 1893; Haldane 1922). His studies were later referred to as the "most fundamental studies and far-reaching contributions to physiology" (Altman 1986, p. 217).

3 Self-Experimentation with Psychoactive Substances

In respect to psychoactive substances, it appears that the first documented systematic SEs have been published by Horace Wood (1869), a physician and professor of botany at the University of Pennsylvania, who won an American Philosophical Society price for his descriptions of SEs using an extract of the cannabis plant.

In 1896, Weir Mitchell, a pioneering American neurologist, began to carry out SEs with the mescaline-containing peyote cactus, which led to the first detailed description of its psychological effects (Weir Mitchell 1896). His experiment awakened a whole new strain of self-experimentation with psychoactive substances that resulted in a significant expansion since the turn to the twentieth century.

Because animal experiments are of rather limited value when it comes to assessing psychological effects, one would expect that research on hallucinogenic or psychedelic substances should have evoked significant self-experimentation by researchers, chemists, and therapists. This was confirmed by a large number of SEs documented in relation to hallucinogens, entactogens, and dissociative drugs, such as ketamine.

4 Defining the Topic

The purpose of this chapter is to highlight the rich tradition of self-experimentation in the field of psychoactive substance research that spans more than a century. For unknown reasons, the topic related to SEs with psychoactive substances, despite having a long-standing tradition in medical research contexts, has not been considered in the authoritative review on medical self-experimentation published by Altman (1986). Due to the large amount of material available, the scope of this chapter had to be limited in two ways:

1. Specific types of psychoactive substances that are considered to produce rather "simple" patterns of effects have been excluded, such as benzodiazepines, antidepressants, simple amphetamine-like stimulants, and (synthetic) opioids/opiates. These substances produce relatively easily predictable psychological effects. Specifically, the spectrum of internal experiences induced by these types of drugs shows a more uniform pattern with rather small interindividual variation (Table 1). It is also obvious from the existing literature that these substances were comparatively less frequently studied in SEs (Fig. 1). This is in contrast to hallucinogens, hashish, and the (somewhat more "complex") psychostimulant cocaine. These substances seem to produce "more interesting," complex, and challenging effects, which include large interindividual variation. Another reason for encountering more SEs with these types of substances might be associated with the eminently subjective character of the experience, which cannot be easily described to someone who has not experienced them.

Table 1 "Simple" and "complex" effects of psychoactive drugs[a]

"Simple" *drug effects*
Increase or decrease of arousal
Hypervigilance or clouding of consciousness
Euphoria
Anxiolysis, relaxation
Decrease of emotional reactivity, memory, self-perception
"Complex" *drug effects*
Pseudo-hallucination, hallucination, synesthesia
Enhanced visual imagery
Intensification of affectivity (euphoria, dysphoria, anxiety)
Alteration of space/time experience
Altered thought processes (less abstract, more imaginative, unusual associations)
Memory changes (hypermnesia, age regression)
Different degrees of ego-dissolution
Mystical-type experiences

[a]It has to be noted that psychoactive substances that induce "complex" effects do not typically induce one or two types of effects but usually involve more than five at the same time, which contributes to the complexity of the subjective effects experienced and reported

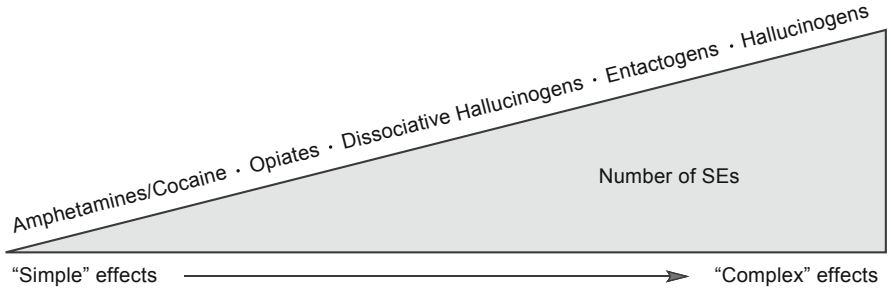

Fig. 1 Increasing complexity of drug effects (left to right) correlates with the amount of documented scientifically driven self-experiments (SEs)

2. Another limitation is that this review will be restricted to SEs performed by physicians, psychologists, or medicinal chemists. In general, information about other groups of researchers in the scientific arena who carried out SEs is rather limited. Clearly, there is an abundance of information available, most notably published by writers, intellectuals, and artists, but an inclusion of this aspect is beyond the scope of this chapter. However, a few examples outside these limits have been included.

4.1 Definitions of Self-Experiments with Psychoactive Substances

As far as self-experimentation with psychoactive substances is concerned, a classification into three types of SEs has been adopted for the purpose of this chapter:

4.1.1 Controlled Self-Experiments

These SEs are usually carried out in a controlled (clinical) environment, are seriously planned in advance, and are conducted with an exactly defined dose. Usually, some knowledge on the effects of the drug is provided in advance. They are usually intended to facilitate some form of systematic self-observation. In most cases, the subject is a physician or a scientist, and an outside observer and/or a person supervising the experiment is also present. Details about the experiment are documented and include information about dose, mode of application, environment, and experimental procedure. Usually, a written self-report is provided by the experimenter. The reasons for this kind of approach can differ. Sometimes, only a one-time test of a substance is of interest. On other occasions, it might be intended to learn more about the subjective experiential pattern induced by a specific substance. In other cases, there may be a desire to learn more about pathological conditions "from inside", for example, by inducing a "psychosis"-like state in the psychiatrist or psychotherapist himself. Most experiments reviewed in the present review chapter belong to this category.

4.1.2 Uncontrolled Self-Experiments

Uncontrolled SEs are those in which a scientist is at first testing a substance on himself, but without giving much detail and documentation on what was specifically done and experienced. Important parameters of the experiment such as its method and descriptions might not be controlled or even completely missed. An outside observer might be present or not. Specific measures or instruments to objectify some of the effects experienced are not used. Nevertheless, the testing might be considered useful for certain purposes, such as self-awareness, insights into the subject's reactions and observations about how to cope with the drug effect, etc. Uncontrolled self-experimentation however suffers from the possibility of obtaining irreproducible results. One potential concern is that uncontrolled SEs might lead to unrealistic and dangerous behavior either during or after the experiment. The subject might also be confronted with a disabled state of helplessness. Other risks might also involve stepping outside the scientific framework and methodology or getting "out of control," for example, by developing drug dependence and thus resulting in a problematic pattern of use and/or adverse psychosocial consequences. Nevertheless, in most cases these dangers appeared to be limited. At the same time, the type of drug used in most of the SEs needs to be considered. For example, hallucinogens and entactogens do not appear to display the dependence potential observed with cocaine or other euphoric psychostimulants (Nichols 2016).

4.1.3 "Wild" Self-Experiments

These are SEs, which are not intended to lead to scientifically relevant knowledge and are therefore, somewhat beyond the scope of this chapter. In this context, experimenters might come from a broad range of backgrounds including problematic drug users in search for another "high." From a historical perspective, "wild" SEs were not commonly encountered in the eighteenth and nineteenth century although some of the early experiments with nitrous oxide (laughing gas) may belong to this category. At the same time, this particular category represents a significant part of less systematically conducted self-experimentation known since the 1960s. Usually, these experiments are not planned as much in advance. They are not primarily undertaken to gain scientific data in the traditional sense. A primary motive can be the testing of a new drug unknown to the person or a testing of purity and dose. Motivations range from curiosity about testing newly appearing substances "for the health of the drug user community" (Soussan and Kjellgren 2014) to a more serious scientific or therapeutic interest and self-treatment. This does not exclude the possibility that the experimenter has undergone significant preparation and that the circumstances under which the experiment is conducted are carried out in a safe and serious fashion.

5 Self-Experimentation with New Psychoactive Substances (NPS)

From the mid-1960s onward, "wild" drug self-experimentation carried out by laymen became a mass phenomenon. However, the earliest origins can be traced back to the 1950s, when some artists and writers began to experiment with drugs, who later became known as "beatniks" (Bisbort 2009). In the early 1960s, "wild" SEs also began to appear in therapeutic and research circles in the USA. A much wider definition of "wild" SEs might include lay use of these substances since the mid-1960s when millions of young people in the USA and elsewhere ingested hallucinogens such as LSD, mescaline, or psilocybin.

During the last four decades, a process of cultural adaption to these drugs has taken place (Henderson and Glass 1994). Legislation, adapted medical treatment, as well as harm reduction through informal learning processes of user groups are placed in this perspective. These developments have limited the distribution of these drugs but also established a "black" market. Due to legislative control of the classic stimulants, hallucinogens, entactogens, and dissociative hallucinogens, drug producers and distributors were eager to develop substances that did not fall under control measures. Eventually, this intention led to the emergence of so-called designer drugs in the early 1980s. MDMA as well as a range of other substances (e.g., synthetic opioids, piperazines, or phencyclidine-based compounds) were examples of these early attempts to circumvent the law (Kirsch 1986; Passie and Benzenhöfer 2016; Henderson 1988; Morris and Wallach 2014).

Since the publication of Shulgin and Shulgin's PIHKAL (Shulgin and Shulgin 1991) and TIHKAL (Shulgin and Shulgin 1997), many new substances started entering the recreational drug market (e.g., King and Kicman 2011; King 2014). In the late 1990s, a new and more organized market of "party pills" and "research chemicals" began to emerge, which was intended to provide uncontrolled alternatives. At this moment, the umbrella term "NPS" typically tends to refer to substances that are not controlled internationally but that may pose comparable threats to public health, which means that they are therefore not listed in any of the Schedules of the United Nations' drug control conventions (Brandt et al. 2014; Evans-Brown and Sedefov 2018). From a practical perspective however (e.g., data collection and monitoring), substances that have been placed under international control more recently still tend to be viewed as NPS. The number of NPS detected globally reached about 800 by the end of 2017, and the diversity of drug classes has increased within the last 10 years (Tettey et al. 2018). Commonly encountered drug classes include psychostimulants, synthetic cannabinoid receptor agonists, entactogens, hallucinogens, dissociative drugs, synthetic opioids, and benzodiazepines (e.g., Dargan and Wood 2013; EMCDDA 2015; Baumann et al. 2017; UNODC 2018; Evans-Brown and Sedefov 2018).

Since information about dose and effect is typically not available, the concept of self-experimentation and of how these experiments are structured introduces an expanded meaning relative to the classification introduced above. For example, they might serve as a "first evaluation" of a substance's unknown effects, its

"most effective" route of administration, and its potential dangers. In order to exchange information about their experiences (and read about those reported by others), substance users refer themselves to specific websites, which are organized in a forum format that allows users to post (frequently unedited) information to help exchanging information on the drugs in question. Normally, there is no explicit design for the experiment, no formal professional education in scientific observation and methodology, and no knowledge of identity and purity of the substances involved. In this context, experimentation might therefore be considered as part of a broadened version of "wild" SEs of the third category (see above).

In respect to SEs with NPS, some additional issues might have to be considered:

1. The time span covering the use of NPS (e.g., 2005–2018) is relatively small compared to other psychoactive substances.
2. The clinical and experimental environment of today does not easily allow for SEs with NPS due to the specific requirements placed on clinical studies (availability of nonclinical toxicological data, good clinical practice, etc.).
3. In countries where implementing self-experimentation with NPS may be more difficult due to existing drug control legislation, people who opt for ingesting NPS cannot normally publish their results in the scientific domain but might place their (non-standardized) "trip reports" in Internet forums.
4. Virtually no detailed SEs with NPS were published in the scientific domain.

Nevertheless, as far as the evaluation of Internet forum contributions is concerned, information about effects of some NPS has been extracted and published using qualitative analysis tools (e.g., Kjellgren and Soussan 2011; Kjellgren et al. 2013; Kjellgren and Jonsson 2013; Soussan and Kjellgren 2014, 2015; Van Hout 2014; Erowid and Erowid 2015; Swogger et al. 2015; Van Hout and Hearne 2015a, b; Hearne and Van Hout 2016; Assi et al. 2017; Abouchedid et al. 2018).

As far as SEs with NPS are concerned, some notable exceptions exist where controlled self-experiments (category 1) have provided valuable information. For example, this was demonstrated for first-generation synthetic cannabinoid receptor agonists (SCRAs) when confirming the psychoactive nature of ingredients suspected to be present in branded "legal highs" (Auwärter et al. 2009). Interestingly, oral administration of the SCRA AM-2201 showed that the compound was not psychoactive at the dose tested (5 mg) and that the metabolic transformation resulted in the formation of some compounds that were also observed to be metabolites detected in closely related SCRAs (Hutter et al. 2013). A variety of challenges arises within a clinical and toxicological context. For example, initial drug-screening procedures based on immunochemical assays are normally not able to identify a specific NPS although sufficient cross-reactivity might exist to enable the identification of a potential drug or drug class. Other analytical difficulties might include the need for targeting the metabolites instead of the parent drug, most notably particular sample matrices (e.g., urine); thus, having data available on the metabolic fate and pharmacokinetic parameters strengthens the ability to identify a newly and previously unknown NPS in biological sample material (Wagmann and Maurer 2018;

Meyer 2018). In addition, it has been frequently noted that the biotransformation of some drugs can result in the formation of metabolites that are both pharmacologically active and which are also medicines in their own right. One of the examples where this has been identified could be found with a number of NPS-based benzodiazepines, and the fact that self-experiments have been carried out to shed light on these phenomena revealed important contributions to understanding these mechanisms. In addition, these experiments revealed significant differences in drug potency and detectability in biological samples over time (Moosmann et al. 2013a, b, 2014; Kintz et al. 2017; Huppertz et al. 2018; Ameline et al. 2018).

However, the consideration of non-standardized experiments resulting in non-standardized descriptions of drug experiences ("trip reports") and discussions on these online forums (e.g., erowid.org, bluelight.org, drugs-forum.com, or reddit.com) is beyond the scope of this chapter. Peer-to-peer generated knowledge and a social support system in respect to knowledge exchange and harm reduction can be important pillars of such a drug discourse, but it is hard to extract and evaluate the quality of those reports from these uncontrolled or "wild" experiments. As the above-mentioned publications have shown, these non-standardized reports from non-standardized experiments can just be taken as anecdotal evidence. Their use in the scientific domain is at best limited to extractions from many reports to gain a rough "mean" impression regarding their usual pattern of effects. At the same time, it is unclear whether these forums also inspire drug taking by providing these descriptions. Many users actively contributing to those forums, including descriptions of their SEs, appear to be experienced drug users driven by a desire for recreation, pleasure, novelty, and a range of functional or compensatory purposes fulfilled with their substance use.

A recent online survey found that motivations for this self-selected sample of NPS users have to be reportedly based on safer and more convenient drug use, satisfaction of curiosity and interest in drug effects, fulfillment of a sense of adventure, promotion of self-exploration and personal growth, functioning as coping mechanism, performance enhancement, facilitation of social bonding and belonging, and a means for recreation and pleasure (Soussan et al. 2018). Obviously, the motivations of users typically differ depending on the substance of choice. Whilst users of hallucinogens and entactogens appear to be mainly oriented toward self-exploration and occasional use pattern, many users of synthetic opioids are seemingly trying to cope with symptoms and clinical features associated with psychiatric disorders including opioid dependence.

6 Self-Experimentation with Various Other Psychoactive Substances

In the following subchapters, an overview on SEs of other psychoactive substances used will be provided. As mentioned before, this review is limited to hallucinogens, entactogens, cannabis, cocaine, and some dissociative hallucinogens.

6.1 Nitrous Oxide

Nitrous oxide or laughing gas was discovered in 1772 by the British inventor Joseph Priestley (1733–1804). In 1799, Thomas Beddoes, a British physician from Bristol, opened a small experimental clinic and laboratory, where he experimented on the therapeutic use of different gases, including nitrous oxide. Based on his first SEs, he got the impression that "... there seems to be quick and wrong alterations in the degree of illumination of all surrounding objects; and I felt as if composed of fine strings ..." (quoted in Shedlin et al. [1973] 1992, p. 11). It was Beddoes who hired Humphrey Davy, a self-educated student of medicine, as his assistant and gave him equipment and encouragement to pursue further experiments (Davy 1800). Davy believed in self-experimentation, which proved to be a pleasurable activity as far as nitrous oxide was concerned, though very difficult to relate and express in scientific terms. After experimenting on himself between 1799 and 1800, he wrote on the subjective experiences. An assistant of Beddoes reported on the challenges faced with the research on these fleeting experiences: "...the nature of the sensations themselves which bore greater resemblance to a half delirious dream than to any distinct state of mind capable of being accurately remembered, contributes ... to increase the difficulty" (quoted from Shedlin et al. [1973] 1992, p. 13).

After having a hard time of producing pure nitrous oxide, Davy saw no other options than self-experimenting with the gas because it was felt that animal experimentation was not considered workable. With a careful scientific attitude, he reports: "I was aware of the dangers of this experiment. ... I thought that the effects might be possibly depressing and painful, but there were many reasons ... to believe that a single inspiration of a gas ... could neither destroy nor immediately injure the powers of life" (Davy in Shedlin et al. [1973] 1992, p. 55). After using very low doses at first, further experiments were undertaken using higher dosage and extended length of administration but in the presence of a physician. When Davy increased the length of administration, "... vivid ideas passed rapidly through the mind, and voluntary power was altogether destroyed." However, he felt an immediate "desire of increasing the pleasurable feelings. ... Sometimes I manifested my pleasure by stamping or laughing only, at the times by dancing around the room and vociferating. ... Sometimes I had the feeling of intense intoxication, attended with but little pleasure; at other times, sublime emotions connected with vivid ideas" (Davy, quoted in Shedlin et al. [1973] 1992, p. 14). Davy first described the pain-relieving properties of nitrous oxide in his book although its potential use as an anesthetic was not discovered until 40 years later.

Following experiments with anesthetics other than nitrous oxide performed over a period of 14 years, philosopher Benjamin P. Blood (1832–1919) claimed that he gained revelatory insights "in which the genius of being is revealed; but it cannot remembered in the normal condition ... there is a comfort of serenity and ancient peace; while for the resolved and imperious spirit there are majesty and supremacy unspeakable" (Blood 1874, quoted in Shedlin et al. [1973] 1992, pp. 73–74). Blood concluded from his research that "the lesson is one of central safety: the Kingdom is within us. All days are judgment days; but there can be no climacteric purpose of

eternity, nor any scheme of the whole. The astronomer abridges the row of bewildering figures by increasing his unit of measurement: so we may reuse the distracting multiplicity of things to the unity for which each of us stands" (Blood 1874, quoted in Shedlin et al. [1973] 1992, p. 76).

The prominent American psychologist, physician, and philosopher William James (1842–1910) came across the writings of Blood and was eager to conduct his own SEs with nitrous oxide (James 1882). In one of his seminal publications entitled *The Varieties of Religious Experience* (James 1902), he described its effects as "revelations of significant metaphysical insights" but found himself unable to remember the exact contents of the experience. Nevertheless, he strongly urged others "to repeat the experiment to gather experiences with this extraordinary state of consciousness." According to James, ". . . the keynote of the experience is the tremendously exciting sense of an intense metaphysical illumination. Truth lies open to the view in depth beneath depth of almost blinding evidence. The mind sees all the logical relations of being with an apparent subtlety and instantaneity to which usual consciousness offers no parallel . . .." However, his enthusiasm seemed limited: ". . . as sobriety returns, the feelings of insight fades, and one is left staring vacantly at a few disjointed words and phrases, as one stares at a cadaverous-looking snow peak from which the sunset glow has just fled . . ." (James, quoted in Shedlin et al. [1973] 1992, p. 77). Following extensive numbers of SEs, James was frustrated with any attempt to measure the experience but concluded ". . . that our normal, waking consciousness, rational consciousness as we call it, is but one special type of consciousness, whilst all about it, parted from it by the flimsiest of screens, there lie potential forms of consciousness entirely different. . . . no account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded" (James 1902). According to historian Mike Jay (2009), nitrous oxide emerged as the first synthetic psychoactive substance that triggered systematic research involving SEs on the nature of the subjective experience.

6.2 Cannabis

It is impossible to nail down when the first SEs took place with this most prominent psychoactive drug that is the cannabis plant (*Cannabis sativa*, etc.) forming the resin hashish. An early nonmedical self-experimenter with this drug was Fitzhugh Ludlow, who ingested large doses of cannabis resin and gave eloquent descriptions of their subjective effects. He also noted correctly the relation between dose and effect, inter- and intraindividual variations in response, and the influence of set and setting. His autobiographical book *The Hasheesh Eater* (Ludlow 1857) created popular interest in hashish in the USA, leading to private hashish clubs. Ludlow also recorded the development of dependence and the subsequent struggle experienced with breaking the habit (Dulchinos 1999).

The studies on cannabis inebriation carried out in the mid-1920s by the German physicians Ernst Joël and Fritz Fränkel were predominantly based on their SEs (Joël and Fränkel 1926). The authors criticized the pharmacopsychological research of

psychiatrist Emil Kraepelin, which were felt to just register isolated measures. Joël and Fränkel were ambitious to contrast this approach with their "method of experimental psychopathology", which looked for influences of psychoactive substances on the "whole person" and their performance. Their SEs were intended to be "an experimental probe into the anomalous life of the soul." Following some initial animal experiments, their SEs revealed a state of intoxication characterized by a steady change between a dreamy and nearly usual waking state. Mood and affects were changing and ranged from feelings of perplexity, fragmentation, feelings of wishless euphoria, or ecstatic rapture. Trains of thought were altered, sometimes enriched by additional associations, sometimes disturbed or interrupted. Memory was found to be dysfunctional. Joël and Fränkel pointed to the "didactic" significance of SEs when used to "produce and observe artificial mental illnesses. Ideally, these drug-effects have to be short-lasting and be free from grave somatic side-effects as well as lasting after-effects" (Fränkel and Joël 1927, p. 83). Colleagues of Joël and Fränkel at the psychiatric clinic in Munich were also conducting SEs with cannabis extracts in the mid-1920s, but did not publish many details (Kant and Kropf 1928). In 1930, psychiatrist Kurt Beringer and some colleagues also conducted SEs with cannabis (Beringer 1932).

6.3 Cocaine

The first scientist to report on SEs with cocaine was the Italian anthropologist, physiologist, and neurologist Paolo Mantegazza (1831–1910). His response to the psychological effects was enthusiastic. "Little by little, one starts to feel that the nervous powers are increasing; life is becoming more active and intense; and one feels stronger, more agile, and readier for any kind of work" (Mantegazza [1859] 1973, p. 38). When he increased the dose, he felt "being isolated from the external world. One also feels deeply joyful and intensely alive." He also increased the dose to the maximum and ". . . experienced the delirium of coca intoxication, and I must confess that I found this pleasure by far superior to all other physical sensations previously known to me. . . . I sneered at the poor mortals condemned to live in this valley of tears while I, carried on the wings of two leaves of coca, went flying through the spaces of 77,438 worlds, each more splendid than the one before" (Mantegazza ([1859] 1973). However, no serious aftereffects resulted from his experimentation.

In 1884, Sigmund Freud, the creator of psychoanalysis, famously conducted SEs with cocaine over a period of years. At first, he ordered several grams of this drug to study its physiological effects after having read about its use by American Indians. In a first SE, 50 mg of cocaine eliminated his bad mood for a day, without decreasing physical or psychical energy (Freud 1884). Coming from this positive experience, he extended his use to treat his well-known melancholia. He enthusiastically recommended cocaine to others (Freud 1885a). Based on his SEs, Freud described "cheered up and persistent euphoria that cannot be differentiated from a normal euphoria observed in healthy people . . . One feels an increase in self-control, more

vigor and more able to work …" (Freud 1884). Freud also lectured about his experiences and his intention to use it on a broader scale (Freud 1885b). At this point in time, cocaine was not known as a recreational drug, and the problem of dependence was not on Freud's mind. Freud concluded that cocaine could be easily applied in cases of "neurasthenia" and melancholia. However, just 2 years later, Freud's euphoria was over when he discovered cocaine's dependence potential.

The American physician Ring (1887) wrote on "Cocaine and its fascinations, from a personal experience" for the purpose of evaluating its risk potential. Originally, he used cocaine for chronic pharyngitis but began to enjoy its euphoric effects and became "dangerously attached to the drug."

Aleister Crowley (1875–1947) was a former medical student and British magician engaged in the use of science to establish more objective methods for magic and for reaching certain states of consciousness. Since the 1910s, Crowley used hashish and cocaine on a regular basis and sometimes mescaline. Cocaine was his favorite drug, as evidenced by his flowery description of its exhilarating effects. Crowley's diaries show that he experienced the full spectrum of cocaine's effects, including unpleasant hallucinations, paranoia, and dependence, which can turn its user into a "slave of cocaine." On the other hand, he pointed to artists as examples for its productive and creative use. However, later in his life, he lost control over his use of the drug (Crowley [1917] 1973).

In the late 1920s, Ernst Joël and Fritz Fränkel also published a significant monograph on its effects and dependence-producing properties (Joël and Fränkel 1924). Their detailed descriptions show an intimate knowledge about the effects of the drug, suggesting that their writings also profited from SEs with the drug. The work based on SEs as well as experiments with artists revealed an elevation of mood and an increase in self-confidence. The intellectual abilities seemed to be subjectively increased although this did rarely led to what is considered as "lasting creations" (Joël and Fränkel 1924, p. 1031). Later SEs included combinations of cannabis with cocaine, and it was found that the effects of cannabis were significantly decreased if not completely eliminated by cocaine (Joël and Fränkel 1929). Both physicians were very aware of the dependence-producing potential of the drug and fought against the black market and illegal distribution. Lewin placed a serious warning at the end of his book chapter on cocaine: "During recent years I have seen among men of science frightful symptoms to the craving for cocaine. Those who believe they can enter the temple of happiness through this gate of pleasure purchase their momentary delights at the cost of body and soul. They speedily pass through the gate of unhappiness into the night of the abyss" (Lewin 1998, p. 74).

6.4 Hallucinogens

6.4.1 Mescaline

In 1896, and following some initial SEs reported by Prentiss and Morgan (1895), the prominent American neurologist Weir Mitchell (1896) performed a SE with two and a half buttons of the mescaline-containing peyote cactus (*Lophophora williamsii*).

He experienced an endless display of richly finished Gothic towers, statues, spinning hoops laden with jewels, and other marvels when he closed his eyes. Interestingly, his critical faculties remained intact during the intoxication phase, when he had the "... decisive impression that I was more competent in mind than in my everyday moods. . . . the sense of increased ability was so notable that, liking to test it . . . I took up a certain paper on psychology, which a week before I had laid down in despair. I grieve to say that it was less to be comprehended than ever. My ignorance would have remained bliss had I not made the experiment" (Weir Mitchell 1896, p. 1626). Weir Mitchell's report inspired Havelock Ellis, a prominent British physician, to carry out a SE with mescaline a year later where he ingested a decoction made from three buttons. His descriptions highlighted significant changes in his visual perception and concluded that ". . .ever since this experience I have been more aesthetically sensitive than I was before to the more delicate phenomena of light and shade and color" (Ellis 1898, p. 134).

Louis Lewin, professor of pharmacology in Germany, and the first systematic explorer of psychoactive substances (Lewin 1924), and Arthur Heffter (Fig. 2), a leading German pharmacologist (and founder of the Handbook of Experimental Pharmacology), were the first researchers who self-experimented with extracts from the mescaline-containing peyote cactus. Experiments on animals were conducted in the first instance in order to learn about physiological reactions and toxicity (Heffter 1894; Lewin 1888). In a series of six elf-experiments, Heffter self-administered different fractions of his plant extracts to evaluate the fraction containing the main active principle (Heffter 1898). Nearly a hundred years later, an institute established for advancing the research on psychedelic substances was named The Heffter Research Institute (www.heffter.org).

Fig. 2 German pharmacologist Arthur Heffter (1859–1925) and founder of the Handbook of Experimental Pharmacology. Courtesy of the Archives of Humboldt University, Berlin (Germany)

The 1920s witnessed many human studies with mescaline. Approximately one third of these experiments were SEs performed by physicians (Passie 2005). A few significant examples should be mentioned in some detail. In 1912, Knauer and Maloney gave mescaline (0.15–0.2 g, im) to nine physicians to compare inter- and intraindividual drug-induced effects. The authors mention that "We may see the whole symptomatology clearer if psychiatrists themselves could live through the experience of psychosis. Since this experience is usually not accessible to us, the only way to induces transitory psychosis is through the intake of such substances" (Knauer and Maloney 1913, p. 426). Guttmann (1921) refers to SEs with mescaline conducted by himself and some of his colleagues. Their aim was to get a grip on "abnormal psychological processes" by observing them in SEs. Guttmann reported cognitive and mental irritation but also elation of mood and transcendence of time and space. He also drew parallels to dreams and hypnagogic states.

In the early 1920s, the prominent German psychiatrist Kurt Beringer commenced his research on the "mescaline inebriation." Before he began to experiment, he took part in a study that tested the influence of mescaline on arithmetic, speech, and memory performance. It appears that physicians at the department volunteered for these experiments (Alberts 1921). Beringer's intention was through the ". . . experimental generation of misperceptions to analyze them more closely through introspection and the changing nature of the experimental conditions" (Beringer 1923, p. 426). Beringer's groundbreaking monograph on the "mescaline inebriation" provided a systematic evaluation of the psychopathological phenomena produced, including 50 self-descriptions obtained from his volunteers (Beringer 1927). Some of his subjects reported exhilarating nirvana-like experiences, which remained significant to them for a long time afterward (e.g., Prinzhorn 1927, 1928). During the 1950s, Beringer's follower, professor Hans Ruffin at Freiburg University, gave assistant doctors a shot of mescaline for a SEs after which they took part in the usual routines on the wards. The volunteers became sometimes quite irritated, and in this case, it was part of the experiment that other (already mescaline-experienced) doctors tried to "talk them down" (Passie 2005).

During the 1920s, the German psychiatrist Konrad Zucker conducted experimental research using different psychoactive substances, including cannabis and mescaline. He considered SEs a requirement for understanding the main features of the state of intoxication and to conduct experiments appropriately (Zucker 1926).

In the early 1930s, the physician and psychologist Hans Friedrichs at Bonn University in Germany conducted experiments in which he collaborated with psychologists who were able to describe the complex experiences induced by mescaline in detail. Friedrichs' experiments included a special feature that made his experiments unique in the early history of research with hallucinogens: "A strict standardization of external experimental conditions was to a large extent abandoned. Through maximal adjustment of the external situation and freedom the individual character of the inebriation should unfold in its own original form" (Friedrichs [1940] 2009, p. 7). His recently rediscovered dissertation on these experiments

represents the most detailed psychological study on the mescaline intoxication up to now (Friedrichs [1940] 2009).

In 1925, the German-born American neurologist Heinrich Klüver ingested some peyote buttons in his laboratory at the University of Minnesota (Klüver 1966). According to himself, he performed this SE "... not for the sake of consciousness expansion or other unique experiences, but to test a new tool possibly useful in studying various problems of the psychology and pathology of perception [and] ... the study of certain types of pseudohallucinations ..." (Klüver 1980, p. VIII).

Psychopharmacologist Roland Fischer began his long career of hallucinogen research with a SE with mescaline in 1945, which was published in the form of a detailed account (Fischer 1946). The professor of psychiatry, Norbert Matussek (1952), at the Max Planck Institute of Psychiatry in Munich (Germany) also conducted some SEs with mescaline and two other physicians to gain insights into the nature of psychotic states. The Canadian psychiatrist Humphrey Osmond was also not shy of performing SEs and took also part in a Native American ceremony in 1956 centered around the ingestion of peyote (Osmond 1970). Similarly, this was also done by two other prominent psychiatrists (Ammon and Patterson 1971).

6.4.2 Lysergic Acid Diethylamide (LSD)

The psychological effects of LSD were discovered in 1943 by Albert Hofmann in the laboratories of the pharmaceutical company Sandoz in Basle (Switzerland). At first, he got accidentally intoxicated in his laboratory and felt some strange sensations. Shortly thereafter, he conducted a SE with LSD and found it to be active in extremely small quantities as low as 0.1 mg. Further SEs by his laboratory co-workers followed soon (Hofmann 1955). Somewhat later, a whole series of SEs was performed by Solms to evaluate the activity of some derivatives of LSD (Solms 1956). It is obvious from the publication on the first clinical studies on LSD that most volunteers were physicians located at the Psychiatric Clinic at the University of Zürich (Switzerland) (Stoll 1947; Condrau 1949). Interestingly, virtually all studies conducted with LSD until the mid-1950s were SEs and/or employed physicians as subjects (e.g., Becker 1949; Mayer-Gross et al. 1951; Weyl 1951; Arnold and Hoff 1953; Frederking 1955).

The psychoactive effects of LSD were discovered and inspired significant research efforts across scientific disciplines, especially in psychiatry. For example, the Canadian psychiatrist Humphry Osmond (who later coined the term "psychedelic" = mind-manifesting) was curious about gaining insights into the subjective world of the schizophrenic mind by taking a variety of hallucinogens (cf. Hoffer and Osmond 1967). In the mid-1950s, Osmond let the internationally prominent writer Aldous Huxley take mescaline under his supervision. Following this experience, Huxley became a major spokesman for the intelligent use of psychedelics (Huxley 1954, 1980).

In the USA, the first researchers who came in touch with LSD in the early 1950s were Max Rinkel and Sidney Cohen who were not shy to experiment on themselves with the new drug. Cohen took the drug in October 1955 expecting to feel catatonic, paranoid, or confused but found himself "... taken by surprise. This was no

confused, disoriented delirium, but something quite different." He described feeling an elevated peacefulness, as if "the problems and strivings, the worries and frustrations of everyday life vanished; in their place was a majestic, sunlit, heavenly inner quietude . . . I seemed to have finally arrived at the contemplation of the eternal truth" (Cohen 1964, p. 107). After having finished three dissertations on psychological testing of subjects under LSD, he wrote: "Though we have been using the available measuring instruments, the check lists, the performance tests, the psychological batteries, and so forth, the core of the LSD situation remains in the dark, quite untouched by our activities" (Cohen 1967, p. 11). Hoping for more articulate reports, Cohen turned to his friend Gerald Heard, a freelance writer in mysticism and popular science. Heard described LSD's effects as "a shift in consciousness" that was "so clearly similar to the accounts given by the mystics that none of us feel able to deny that this is in fact the experience which we undergo" (Heard, quoted in Novak 1997, p. 93).

Another significant figure in early LSD research in therapy and creativity was the Californian psychiatrist Oscar Janiger. Following Janiger's first SE with LSD in 1954, and more than 10 thereafter, he set up a "naturalistic study" involving 875 people who had been introduced to LSD with many of them being part of the creative community in Beverly Hills and Hollywood, including Anais Nin, Cary Grant, and Jack Nicholson (Stafford 1990).

In the early 1950s, experimentation with LSD began at the Psychiatric Research Institute in Prague (Czechoslovakia). One of the first subjects to self-administer the drug was the internationally known psychiatrist and LSD therapist Stanislav Grof. Sitting in front of a strong flicker light during the initial phase of the experiment, he was catapulted through eons of time and space and felt his consciousness expanded beyond all boundaries. After the Prague spring in 1967, he left for the USA and led the last research center for the therapeutic use of psychedelic drugs in Baltimore, Maryland, until 1976. At this center, psychiatrists and nursing personnel were involved in SEs aiming to learn both about their patients' psychotic crises and also therapeutic processes (Grof 1980).

In 1959, LSD was at its peak of medical acceptance although Cohen detected trends of going lax in controlling the drug and its use. Researchers immersed in SEs began to share LSD in their homes and introduced others to the experience. In 1958, it was reported that researchers held "LSD-25 social parties" and that LSD became "an intellectual fun drug" (Ditman, quoted in Novak 1997, p. 99). In the late 1950s, prominent (and CIA-associated) LSD researcher Harold Abramson held Friday-night soirees in his home and was "besieged by people who wanted to take the drug" (Abramson 1967, pp. 33, 475; cf. Novak 1997, p. 99). In 1960, Cohen felt very much "uncomfortably unscientific" and wrote to his sponsor that he got enough "of the fringy goings on with this group of drugs." The Federal Drug Administration's first investigations on the abuse of LSD began in 1961 in Southern California, where "reports of misuse" focused on "physicians and psychologists who were not authorized to use the drug" (Novak 1997, p. 108). In 1962, the police raided several therapists using LSD in the Los Angeles area and seized their LSD supply. However, a well-informed psychiatrist working for the US Army stated: "in the early 1960s,

practically every LSD investigator in the nation had taken LSD at least once, if only to become familiar with the subjective effects. Many, of course, took it innumerable times, incorporating it into their life style and self-concept" (Ketchum 2006, pp. 67–68). Ketchum also performed a SE with 80 μg of LSD in 1965, but without reporting significant insights (Ketchum 2006).

In 1961, some physicians and pharmacologists at the Psychiatric University Clinic in Zürich conducted systematic SEs to compare the effects of LSD, psilocybin, and ethanol. The experiments were recorded on tape and used later in lectures about the effects of drugs (Waser 1990).

Since the late 1950s, psychologist van Dusen (1961) conducted SEs with LSD at the Mendocino State Hospital in Talmage, California (USA). He concluded "there is a central human experience which alters all other experiences. . . . I wish to draw attention to the fact that the still experimental drug . . . (LSD) appears to facilitate the discovery of this apparently ancient and universal experience" (van Dusen 1961, p. 11).

A group around professor of psychology Timothy Leary commenced research into the psychological effects of psychedelics after they had conducted SEs with psilocybin in 1961. They administered psilocybin in a "supportive environment" to volunteers. In some experiments, an experimenter took the drug together with the experimental subjects (Leary et al. 1963). A short while later, their ambitions to propagandize "consciousness-expansion" became so impertinent that they left Harvard University for conducting social experiments. The group opened a "psychedelic center" in Zihuatanejo (Mexico), where they explored regular psychedelic drug use and experimental social ways of life (Downing 1965). Thirty-five people, mostly psychologists, studied "the transpersonative effects of group interaction with the concurrent use of LSD." The group promoted the view that "stereotyped learned patterns, or 'games', created by familial and social pressures . . . are considered to inhibit direct person-to-person contact" (Downing 1965, p. 150). After leaving Mexico, the group opened a center for "psychedelic exploration" in Upper New York. There the group continued working on SEs and began to proselytize, to "turn on the world," feeling that the psychedelic experience furthers a new consciousness which would be leading to a "new age" (Hollingshead 1973). With their "wow"-approach, the group soon attracted the attention of the media, the world, and finally the police. Partially as a result of this, most hallucinogenic substances became controlled in 1966 in the USA.

In the 1950s, physician and neuroscientist John C. Lilly began experimenting with the "isolation tank," in which a person is completely isolated from any sensory perception while being immersed in a salt water solution heated at body temperature. After getting accustomed to these special circumstances, Lilly conducted SEs with LSD in the tank. The resulting books later became classics in "consciousness expansion" and the "spiritual search" literature of the 1970s (e.g., Lilly 1972a, b, 1978).

Dozens of Czech psychology students underwent LSD experiments under the supervision of psychiatrist Stanislav Kratochvíl's team at the psychiatric hospital at Kromeriz. The group's approach focused on didactic and autognostic sessions.

Kratochvíl and his team believed that there is "a significant purpose of the didactic experiments for understanding some mental states occurring during psychosis; for enabling the study of psychopathology at a graduate and postgraduate level; for expanding the understanding of oneself; and for personal growth" (Kratochvíl S, Užití LSD v psychiatrické léčebně v Kroměříži v roce 1966 [The use of LSD in the psychiatric hospital in Kroměříž in 1966]. Unpublished document, 1967, p. 1).

It has to be mentioned that all physicians who founded the Swiss Physicians Society for Psycholytic Therapy (SÄPT) in 1986, which still exists as a knowledgeable institution today, carried out many SEs with LSD, mescaline, psilocybin, and MDMA (Benz 1989).

6.4.3 Nightshade Hallucinogens

When it comes to the somewhat rarely used traditional plant hallucinogens of the nightshade family (*Datura* spp., *Atropa belladonna*, *Hyoscyamus niger*, etc.), which contain scopolamine and hyoscyamine (easily converted to atropine) with hallucinogenic properties, SEs have been rarely reported. That might be due to the fact that the intoxication provoked by these plants induces rather unpleasant physiological and psychological effects. Konrad (1888) and Klinke (1889) conducted the first scientifically driven SEs with scopolamine to explore the effects. Prominent psychiatrist Oswald Bumke (1903) at the University of Munich (Germany) conducted SEs with low doses of scopolamine. The studies of research psychiatrist Hans Heimann, which led to the only monograph on effects of scopolamine, were based on SEs he had conducted to design his study (Heimann 1952). Another focus about the nightshade plants were the "witches ointments" (Hexensalben), which have been used by medieval witches to "travel to the sabbath". In the early 1950s, German ethnologist Will-Erich Peuckert prepared such an ointment following a recipe provided by Giambattista della Porta and smeared it on parts of his body. He recounted afterwards: "We had wild dreams. Horrifically distorted faces danced in front of my eyes. I then suddenly had the feeling of flying through the air. The flight was interrupted repeatedly by massive plunges. In the final phase . . . the image of an orgiastic celebration with grotesque sensual excesses" (Peuckert cited in Wellen 1986, p. 158). Similar experiences have been reported by another self-experimenter using such a preparation (Ferkel 1954).

6.4.4 Fly Agaric (*Amanita muscaria*)

In 1967, Swiss pharmacologist Peter G. Waser and psychiatrist Jules Angst performed SEs with some compounds isolated from the fly agaric mushroom (*Amanita muscaria*). Muscimol and ibotenic acid reportedly produced hallucinations, disturbances of consciousness, as well as time and space perception. Especially remarkable was the perception of "gliding through infinite spaces like on ice and to repeatedly re-experience the situations and sounds in reverberating images." These investigations confirmed the experiences reported from Siberian shamans and their use of this mushroom (Waser 1990, p. 57).

6.4.5 *Salvia divinorum*

The hallucinogenic effects of the Mexican sage *Salvia divinorum* were first reported by the Swedish anthropologist Jean Bassett Johnson in 1938. In the late 1950s, ethnomycologist Robert G. Wasson and LSD discoverer Albert Hofmann took part in a shamanic ceremony by chewing the leaves. They reported mild hallucinogenic effects (Hofmann 1979). Quite a while later (in 1979), researchers took part in another ceremony where a higher dose was given that resulted in more pronounced hallucinogenic effects. In 1982, the active principles (salvinorin A and B) were isolated. Since then, administering higher doses became a possibility, and researchers began to use highly concentrated extracts in SEs to discover powerful hallucinogenic effects and alienating dissociative states. Through SEs, researcher Daniel Siebert found that salvinorin A was not orally active but that it required absorption through the mouth mucosa (Siebert 1994). It is also very effective when smoked. According to reports, salvinorin A effects enter with an irresistibly powerful force that takes the user in a dissociative trance state. After some initial body effects, the user is catapulted into strange realms of experiences. Sometimes, experiences might involve the most cosmic, wonderful, and detailed universes, while at other times, memories might not be recalled. A drastic shift in sense of identity and conscious perception has been reported, usually completely dislodged from the usual body experience and the familiar sense of self or ego. Sometimes, it appears that one has ceased to exist as a body, human, or soul. Some feel a sensation that their "being" can literally enter and inhabit various objects (Siebert 1994; Turner 1996). It appears that virtually all significant researchers of *Salvia divinorum* and its active principles have engaged in self-experimentation (Wasson 1962; Valdes et al. 1982; Siebert 1994; Turner 1996; Arthur 2008). It is noteworthy that this plant/substance does not show any dependence potential, and many users appear to stop its use when confronted with an unpleasant experience (Gonzalez et al. 2006; Maqueda et al. 2015).

6.4.6 *N,N*-Dimethyltryptamine (DMT)

Not much can be said about SEs performed with DMT and closely related substances. Some marginal self-experimentation was going on with these substances during the 1950s and 1960s. Stephen Szára and colleagues (see below) relied on SEs to explore the "psychopathological" effects of DMT and some of its derivatives, which were suspected to be linked to "pathological metabolites" and psychotic states.

Szára took mescaline in 1955, and when he was unable to obtain LSD, he turned to DMT for further experiments. After experiments with cats, he discovered that DMT was inactive when given orally, thus deciding to administer the substance intramuscularly. He described that "The hallucinations consisted of moving, brilliantly colored oriental motifs, and later I saw wonderful scenes altering very rapidly. The faces of the people seemed to be masks. My emotional state was elevated sometimes up to euphoria … My consciousness was completely filled by hallucinations, and my attention was firmly bound to them" (Szára 1957, p. 462). The researchers experimented with different modes of administration and were able to describe a comprehensive clinical picture of DMT's psychological effects (Szára

1957). It became obvious through these SEs that the intensity of effects was significantly linked to the route of administration with nasal insufflation and smoking leading to the most drastic experiences. Later on, Szára also tested closely related hallucinogenic tryptamine derivatives on himself. According to Szára, the effects of these drugs supported "the aminotoxic and indole theory of schizophrenia" (Szára 1961).

One might also mention the SEs with DMT carried out by Timothy Leary. Leary got some intramuscular injections of DMT in 1965: "Suddenly I opened my eyes and sat up . . . the room was celestial, glowing with radiant illumination . . . light, light, light . . . the people present were transfigured . . . god-like creatures . . . we were all united as one organism. Beneath the radiant surface I could see the delicate, wondrous body machinery of each person, the network of muscle and vein and bone – exquisitely beautiful and all joined, all part of the same process" (Leary 1966, p. 86).

As it appears from these SEs, the state of consciousness experienced during the initial intoxication is characterized by amazing visual effects. However, this seemed to be just a prelude to a profound state in which subjects report contacts with "another realm of reality" in which they might encounter discarnate, nonhuman alien beings. "I passed abruptly through to another realm, losing all awareness of my body. It was as if there were alien beings there waiting for me, and . . . spoke to me as if they had been awaiting my arrival. . . . the entities approached me from the front, rapidly and repeatedly, appearing to enter and pass through me" (Meyer 1993, p. 43).

Administrations via intravenous, inhalation, or nasal routes invariably lead to experiences usually so bizarre and dramatic that an inexperienced person might feel like being catapulted out of any known realm of consciousness. Referring to the impression of encountering "discarnate entities in another realm of reality," Peter Meyer elaborated on these encounters following his SEs and those of others (Meyer 1993). A similar direction was pointed toward the research of ethnobotanist and anthropologist Terence McKenna, who experimented with LSD, psilocybin, and DMT. McKenna became a prominent spokesman of the "psychedelic movement" during the 1990s and thereby facilitated the research and distribution of psilocybin (Oss and Oeric 1976) and DMT (McKenna 1991).

More controlled and comprehensive SEs were reported by the ethnopharmacologist Jonathan Ott. He also explored the possibilities of producing an orally active DMT-containing inebriant. Ott's research focused on possible plant mixtures other than those used in the Amazon basin associated with ayahuasca, commonly represented by specific DMT-containing plants (usually *Psychotria viridis*) combined with plant-based monoamine oxidase A inhibitors (normally *Banisteriopsis caapi*) that would render DMT orally active (Ott 1994). Ott carried out hundreds of SEs that he called "subjective bioassays." He later continued his research to explore the psychoactive effect of bufotenine (5-HO-DMT). Ott evaluated different routes of administration and found that some were more effective than others (Ott 1994, 2001a). Even though Ott was not associated with any specific university environment, his SEs followed a scientific format including influential publications in scientific journals (e.g., Ott 1999, 2001b, c).

6.4.7 Synthetic Hallucinogenic Phenethylamines

One follower of Shulgin's research can be seen in the Swiss chemist Daniel Trachsel, who published various contributions on many new psychoactive substances and their effects (Trachsel 2011, 2012; Trachsel et al. 2013). Experimental results about their psychoactive effects are included, but the author distanced himself from any SEs (Trachsel 2011, p. 12).

More ambitious explorations of subjective effects elicited by a series of new psychoactive substances developed by Shulgin were conducted by his close associate and psychologist, Myron Stolaroff. Following SEs with LSD in the mid-1950s, Stolaroff became involved in scientific research on psychedelics. After the control of most psychedelic drugs in the 1970s, Stolaroff conducted SEs with newly synthesized psychedelics 2C-B, 2C-E, 2C-T-2, 2C-T-7, 2C-T4, 2C-T-21, and MEM but also MDMA. Besides Shulgin, Stolaroff was the first who systematically explored the psychological states and their possible uses but under noncontrolled conditions (Stolaroff 1994). He understood his research as an attempt "to make the unconscious conscious" and to give some "guidelines for the proper and safe use of psychedelic drugs in therapy and for spiritual growth" (Stolaroff 1994, pp. 13–14).

6.5 Entactogens/Empathogens

When it comes to the entactogenic drugs, i.e., certain types of ring-substituted 1-phenylpropan-2-amines, it is interesting to see that this group of substances was mainly explored by chemists and pharmacologists.

The first person to experience the psychoactive effects of an entactogen was the Californian chemist and pharmacologist Gordon A. Alles. Alles discovered the psychoactive effects of amphetamine in a SE in 1925. While being interested in researching some amphetamine derivatives in 1934, he accidentally ingested a larger dose of 3,4-methylenedioxyamphetamine (MDA), which marks the first human entactogenic trip. It appears that he did not make this discovery public, because of interest that might arise from the military to be used as a potential "truth drug" useful for interrogation purposes (Passie and Benzenhöfer 2018). However, in 1959, a description of his SE appeared (Alles 1959). In the course of his secret work for the US Army, Alles synthesized other hallucinogenic/entactogenic derivatives of mescaline and probably tested them on himself.

The American chemist and pharmacologist Alexander T. Shulgin started his research on the synthesis and self-administration of psychedelic drugs after having experienced the effects of mescaline in 1960. Shulgin, most probably following Alles' research, first synthesized MDA in May 1961 for the purpose of self-administration. Since that time, Shulgin synthesized and tested (mainly on himself) hundreds of new psychoactive substances of the phenethylamine, amphetamine, and tryptamine class. After initial SEs with a newly synthesized substance, he invited some friends and fellow researchers (more than half of them scientists eager to carry out SEs) to participate in these "trials" to investigate their subjective effects (Shulgin and Shulgin 1991, 1997). In the course of these experiments, Shulgin developed a

simple rating scale in an effort to measure the intensity and the general character of the experiences (Shulgin et al. 1986). However, some scientists suggested that he biased his subjects by informing them about the general character of the substance's effects in advance. Certainly, a comparison with double-blind, randomized, placebo-controlled trials cannot be made, but Shulgin and his associates experimented in their circle for more than 25 years in a kind of systematic fashion, and many results were published in a scientific format (Shulgin and Shulgin 1991, 1997).

An interesting anecdote is that Shulgin was not able to detect the special entactogenic effects of MDE and MDMA in his (self-)experiments. Regarding MDE, his associate, the Chilean psychiatrist Claudio Naranjo, reported "no reaction" in 1967, with a low dose of MDE. Probably because of this report, no further research in the methylenedioxyamphetamine class was conducted. However, in 1975, Shulgin was contacted by a student about the idea of preparing *N*-methyl-MDA (MDMA). The product was considered "interesting" (Resnikoff 2018), but did not lead to much further testing. When Shulgin was informed by another student about the special effects of MDMA in 1976, he commenced with SEs but named its effects in his laboratory notebook as "an alcohol-like intoxication" (Benzenhöfer and Passie 2010). It was not until his friend and psychologist Leo Zeff reacted differently to a higher dose that MDMA became known to a larger circle of psychotherapists (Stolaroff 2004). However, this "failure" shows that self-experiments are subjective, provide just anecdotal evidence, and not rarely lead to wrong conclusions. Shulgin and his wife Ann let the world participate in their research by their inspirational writings (Shulgin and Shulgin 1991, 1997) and enjoyed astonishingly good health in their later years. Noteworthy is Shulgin's first synthesis, SE, and description of the subjective effects of 2C-B (Shulgin 1975).

Long before Shulgin's books were published, the physician Andrew Weil gave the first concise description of the psychoactive effects of MDA (Weil 1976) based on SEs. Weil also conducted SEs with psilocybin mushrooms and the DMT-containing "Yage" plant concoction (Weil 1980). At the same time, further work on the subjective effects of the enantiomers of MDMA and MDA, involving SEs, was published (Anderson et al. 1978). Virtually all physicians and psychologists who used MDMA in psychotherapy in the 1977–1985 period (when it was still legal) reported that SEs inspired their therapeutic work (Passie 2018).

6.6 Dissociatives (Ketamine)

In his autobiographical work "The Scientist," physician and scientist John C. Lilly described his SEs with ketamine and spread the word about its effects. Lilly suggested that ketamine enabled him to "look across the border into other realities" and to venture beyond the social consensus reality to more profound "meta-realities." Lilly also combined the use of ketamine with the flotation tank. Following experiments with electrodes and monkey brains, Lilly explained that ". . . eventually I will use myself as the subject of the experiment . . . until one is willing to undergo the experiment oneself, one must not perform them on other humans. . . . A doctor

should never give a drug to a patient until he has tried it himself" (Lilly in Kelly 1999, p. 48). However, Lilly's use of ketamine became excessive and he was temporarily diagnosed as paranoid. He believed in an "Earth Coincidence Control Office," designed by extraterrestrials to choreograph coincidences to gently push mankind down the evolutionary path.

In the late 1970s, the anesthesiologist Howard Alltounian and his wife, the yoga and astrology teacher Marcia Moore, began to explore the psychedelic effects of ketamine. During their ketamine SEs, they felt a blissful state they called *samadhi*, which subsequently led to the design of a psychospiritual treatment technique called "samadhi therapy," where they introduced these states to others for therapy and "enrichment of spiritual life." They came to believe "that in the right hands this substance could be safely, easily, and advantageously applied toward the psychospiritual regeneration of planet earth." Besides their SEs and some case histories, the authors also discussed some critical issues (Moore and Alltounian 1978). Nevertheless, a few years later, Marcia Moore disappeared and was found dead and frozen months later thought to be a consequence of an accident caused by unrealistic behavior associated with her use of ketamine.

The research by Karl Jansen, an expert on the psychedelic use of ketamine and ketamine dependence ([2001] 2004), was inspired significantly by his own SEs (Jansen and Darracot-Cankovic 2001). His scientific inquiries included photo-imaging of receptors related to ketamine experience and similarities to near-death experiences. His expertise on "ketamine addiction" was expressed in scientific articles (Jansen 2000; Jansen and Darracot-Cankovic 2001), but did not prevent him from becoming ketamine dependent himself. Therefore, the fate of Jansen, Lilly, Moore, and Alltounian point to the dangers of losing control without external control mechanisms in place in situations where self-generated SE gets "uncontrolled". This appears to be especially true when the drug has enjoyable, euphoric, or escape-promoting "dissociative" effects like ketamine. It is noteworthy that in contrast to ketamine, documented SEs carried out by scientists and descriptions of effects induced by the related drug phencyclidine (PCP or Angel Dust) and its derivatives do not appear to be available.

7 Discussion

It appears obvious that some of the first "proto-scientists" who systematically navigated the complex space linked to the use of psychoactive substances were shamans. However, nothing is really known about SEs with psychoactive drugs until the mid-eighteenth century, which triggered a long-standing tradition throughout the nineteenth and early twentieth century. However, it also appears that they became less frequent (and in most cases better controlled) after World War II.

One has to be reminded that after the turn to the twentieth century, medical research was frequently considered a "hobby" for doctors with independent incomes, and research was often seen as a luxury rather than a necessity. Prominent examples for these "private laboratory" researchers include the German pharmacologist Louis

Lewin, the American ethnomycologist Robert G. Wasson, and the American chemist Alexander Shulgin.

In this chapter, the broad range of self-experimentation with psychoactive substances since the mid-1850s is presented. These experiments began to develop slowly and on an occasional basis with the first psychoactive substances to become known in the West being cannabis and cocaine. As outlined in the present chapter, motivations, intentions, "experimental procedures," as well as the trajectories related to these SEs were quite different.

SEs require a willingness to engage in research by trial and error and to be prepared for facing potential health risks. To take this risk might become easier when certain rewards can be expected. Potential rewards might include the prospect of learning more about oneself by means of perceptions beyond the usual mental framework (seen, e.g., with psychedelic and entactogenic drugs), heightened mood, or euphoria (e.g., the euphoriant cocaine or some phenethylamine/amphetamine-based stimulants). As far as the literature published by scientists is concerned, it appears that substances with a comparatively "simple" spectrum of effects (e.g., benzodiazepines and opioids/opiates) have invited much less self-experimentation compared to drugs with more "complex" effects that impact on many spheres of the human experience (e.g., classic psychedelics) (Fig. 1).

The prospect of potentially confronting unpleasant effects such as confusion or loss of self-control (e.g., elicited by nightshade drugs atropine and hyoscyamine) presumably makes it less likely to engage in self-experimentation unless specific purposes have been identified (e.g., evaluating witches' ointments and potions). It is also obvious that experimenters did not tend to repeat them due to these unpleasant side effects. At the same time, it also seems that the classic hallucinogens radiated some form of appeal, at least to some experimenters in spite of the possibility of experiencing psychological effects that might be challenging to cope with. In comparison with other more popular substances, such as the psychostimulants that induce predictable effects, many self-experimenters might not want to be confronted with unfamiliar aspects of their personality and life experiences which, together with the somewhat incalculable course of effects, seems to restrict the use of this class of drugs perhaps to more specific user populations.

This is different with substances that regularly heighten mood, euphoria, and ego-inflation (e.g., cocaine), which have sometimes unfolded their dependence-producing properties in investigators who started the research with other intentions. Escapism ("from reality") might also play a role. A prominent example was John C. Lilly who withdrew from reality when he injected himself daily with ketamine (while lying in an isolation tank) for more than a year. However, this seems to be the exception to the general rule, which is that scientists remained in control of their self-experimentation.

7.1 Motives for Self-Experimentation

Many different motives and backgrounds can be identified when exploring the available literature on SEs with psychoactive substances. Most motives can be found in just only a very few cases and sometimes in combination, whereas others are more common. Some of the common motives include:

- Personal curiosity (Ellis)
- To explore the effects of unknown substances (Hofmann, Solms, Internet forums)
- To learn about drug effects (Beringer, Friedrichs)
- To learn how to handle the substances' effects (Hoffer and Osmond)
- To gain knowledge from the substances' effects (Davy, James)
- To search for answers to philosophical questions and inquiry (Blood, Hofmann)
- To explore new territory (Shulgin)
- To cope with psychological problems (Freud, Lilly)
- To gather power over others (Crowley, US Army)
- To learn how to manipulate others (Crowley, US Army)
- To use and risk one's own organism first (Shulgin)
- To explore possible risks (Grof, Passie)
- To optimize environments used for experiments (Passie)
- To gather information about adverse effects as harm reduction (Internet forums)
- To explore possible complications ("prepared anticipation") (Internet forums)
- Escapism (Lilly, Jansen)

Some substances serve certain purposes better than others. For example, some of the dissociative anesthetics might be more conducive to escapism, which induce a decoupling of the individual from the surrounding world (Feldman et al. 1979). In contrast, cocaine permits an "escape from reality" in respect to a more egocentric and euphoric state of mind but without profoundly altering perception of ego or reality. However, it is also probably fair to state that hardly any psychoactive substance carried such a philosophical underpinning in the way it was expressed for LSD. LSD was advocated as having a purpose other than simply "getting high". For its users, the "psychedelic experience" was about enhanced and expanded perception or "consciousness expansion." "My exponentially heightened awareness saw *through* the static, one-dimensional, ego-constricted, false front which is the consciousness-*contracted* reality of the everyday world. This was no evasive flight *from*, but a deep probe *into* reality" (Solomon 1964, p. X). LSD appeared to provide access to a numinous space unmediated by a religious hierarchy or sacred texts. Therefore, its use was predominantly experimental. A problematic pattern of repeated use was rarely, if ever, reported. In general, it appeared that substances, which "open the mind" to more emotions and unusual perceptions, were less likely to be abused because these types of substances might confront the researcher with an experience and psychological material that might be considered unpleasant and/or irritating. However, controlled and specific conditions, for example, as part of psychotherapeutic interventions, might be specifically sought after and useful.

7.2 Goals of Self-Experiments with Psychoactive Substances

From the review of the literature, a number of goals associated with self-experimental use were identifiable, and some of these were more, whereas others were less explicitly stated. The following list is meant to provide some ideas about the motives and conscious decisions made by those researchers who engaged in SEs. Some should perhaps be seen in the context of incomplete scientific knowledge and methodology:

- To identify the psychoactive constituent(s) in extracts obtained from a plant matrix
- To evaluate the general effects of the substance
- To investigate the metabolism and pharmacokinetics of a substance
- To explore risk potential
- To evaluate some specific effects of the substance
- To start a career in experimental psychopharmacology
- To explore substances with therapeutic potential
- To understand therapeutic processes of patients under the influence of the drug
- To gain personal insights into "abnormal mental states"
- To handle patients in psychotic states with more empathy
- To collect material about intoxication and to instruct students and trainees
- To explore experimental procedures from the subject's perspective
- To design appropriate experiments
- To optimize procedure and atmosphere for experiments
- To prepare for dangers potentially arising from the drug
- To evaluate new psychoactive substances for dissemination to others
- To gain philosophical insights
- To gain mystical states and insights into the human condition
- To enjoy the effects of the substances
- To enhance the drug experience
- To hold social LSD parties

7.3 Ethical Issues in Self-Experimentation with Psychoactive Substances

Not many explicit ethical statements can be found regarding self-experimentation with psychoactive substances. It appears that most of the investigations were triggered by curiosity and/or were part of larger scientific studies that included SEs (e.g., Beringer's investigations with mescaline at Heidelberg University). Systematic explorations of newly synthesized substances also provided an impetus (e.g., Shulgin).

It has to be mentioned that under the conditions operating today, SEs with psychoactive substances under controlled conditions have to be reviewed and permitted by institutional review boards (IRB) that check for compliance with ethical and scientific standards. Essential toxicological data are also required. Few

exceptions from this rule are possible depending on different laws being in force in different countries.

Ethical considerations might have played a role in SEs designed to gain insights into the condition of the mentally ill, and an important implication was to treat these patients more effectively (e.g., Ruffin at Freiburg University, Hoffer and Osmond 1967). Others were intended to develop more empathy for people experiencing psychotic states, for example, as expressed by the founder of the Soteria treatment concept applied to acute psychotic patients (Calton et al. 2008), which were inspired by their own LSD trips (Mosher 1999).

Other SEs were thought to provide insights into the treatment of patients who were treated with LSD- or psilocybin-assisted psychotherapy. Hanscarl Leuner, a "psycholytic" therapist at Göttingen University (Germany), and other like-minded psychotherapists confirmed that psychotherapists wanting to engage in hallucinogen-assisted psychotherapy had to have experience themselves in order to effectively guide patients empathically through their experiences (e.g., Passie 1997; Winkler and Csémy 2014; Grof 1980). From an ethical perspective, this has been considered as an important cornerstone of therapeutic work.

SEs with LSD were also consistent with recommendations made by the Sandoz pharmaceutical company (former Swiss producer of LSD) and were well integrated among psychiatrists and psychologists (Grof 1964). This was also congruent with the psychoanalytical tradition, in which the trainee had to go through a "teaching analysis" in which one was analyzed by an educated psychoanalyst. The purpose of this was to deepen the understanding of reaction patterns and identify "blind spots" as well as deepening the therapeutic process itself. "Auto-experimentation is a way to broaden and complement scholarly knowledge as well as to enrich and deepen a medical doctor' s understanding of those with mental illness; it is possible to say that it contributes to a more humane relationship to those with psychosis" (Roubíček 1961, p. 81).

Passie (2002) has taken part in controlled scientific experiments with psychoactive drugs prior to performing clinical studies in an effort to explore the space encountered during the drug experience. The purpose of this approach was to develop optimization strategies for the research setting and to minimize the occurrence of unpleasant experiences. The experiences resulting from such SEs informed the design of the studies and provided optimal circumstances, which are also paramount to avoiding "bad trips." This is somewhat congruent with the mode of experimentation used very early by Friedrichs ([1940] 2009), Leary et al. (1963), and McGlothlin et al. (1967). It is probably fair to assume that it is not just coincidence that all those experimenters, which provided "optimized" psychophysical environments for their subjects, had profited from SEs, which then informed their modus operandi.

7.4 Kinds and Consequences of Self-Experiments

When evaluating the three kinds of SEs identified earlier, i.e., controlled SEs, uncontrolled SEs, and "wild" SEs (Sects. 4.1.1, 4.1.2, and 4.1.3), it would appear

that the majority of the presented SEs reviewed in this chapter belonged to the first category.

Other examples however seemed to fit into the second category (e.g., Crowley, the Los Angeles group of psychotherapists, and Leary's group at Harvard). It seems that most of those researchers started with scientifically ambitious procedures first but then became successively more and more involved with the drug and its effects until the point when they withdrew from scientific conventions and turned to a somewhat "socially autistic" mode of experimentation. This obviously happened with Leary's group that "dropped out" of science and society. As far as researchers were concerned who operated on a more individual level (e.g., Crowley, Lilly), one cannot help but draw parallels with a similar kind of "autistic" syndrome.

At the same time, experimenting with certain types of psychoactive drugs can be associated with unique features and results. For example, the use of classical hallucinogens such as LSD or psilocybin, in no small part due to the often dramatic nature of the experiences induced, has been associated with changes of personality, social attitudes, and value system. In some cases, self-experimentation has led to alterations of group dynamics (e.g., Leary's group). A similar phenomenon has been observed with a leading psycholytic therapist operating in Switzerland, who founded a sect involving psychedelic substances spearheaded by him as its guru (Widmer 1997). Some observers have interpreted this as a necessary consequence derived from the experiences and insights gained from the use of psychedelic drugs, whereas others have interpreted this "drop out" behavior as a loss of control and a problematic, even dangerous behavioral change. However, this "drifting out of science" phenomenon was associated with a repeated pattern of drug use and a transition into a "wild" form of self-experimentation. However, the published data indicate that such a development was an exception rather than the rule.

7.5 Dangers of Self-Experimentation

The pursuit of self-experimentation has been repeatedly criticized for overenthusiasm, (usually) for positive bias involving data interpretation, and for lack of ability to evaluate the findings critically. As Beecher stated: "... self-experimentation is an unwise performance whenever judgement can enter into the conclusion drawn" (Beecher 1959, p. 468). The researcher involved in research is the experimental subject and the observer at the same time, especially if one aims to probe subjective psychological effects. In conventional experiments, this would be seen as a significant bias. "An enthusiastic investigator's subconscious interpretation of the results of a study in which he is an objective observer, and not a participant, could bias his study to the same degree as it would if he had included himself among the subjects" (Altman 1972, p. 351). When it comes to the study of effects other than the "subjective," for example, when performing a surgical procedure or treating an experimentally induced infection, then this might be considered a much smaller issue.

Another important point is the incalculable risk of experimenting with substances for which no basic toxicology data exist. This might be not have been as risky with substances used for SEs in the past, where for most of them, traditional human use for longer periods of time was reported (e.g., mescaline, cocaine). Especially if it comes to recently emerging NPS, no such "pretesting" exists, and the user is at high risk of overdoses, complications, and psychiatric sequelae.

A list of the possible risks associated with self-experimentation includes the following:

- Overly subjective (e.g., exaggerated) description of effects
- Lazy attitude without realizing potential dangers
- Reckless experimentation
- Loosing contact with consensus/social reality
- Unrealistic behavior
- Losing control over drug use
- Psychological complications
- Physical complications
- Overdose
- Development of dependence
- Drug taking takes center stage
- Group dynamics becomes dysfunctional
- Inspiring others to take a certain substances ("proselytizing")

In general, most SEs carried out in the fields of medicine seemed relatively simple and harmless (e.g., drawing blood, inserting a tube into the gastrointestinal tract, ventilation tests, etc.), and it appeared that these experiments have rarely resulted in significant damage to the experimenter (Altman 1986). The literature reviewed in this chapter suggests that virtually no serious physical complications have been reported, especially when the drugs in question were not taken on a regular basis. But there were exceptions from this rule, and a particular tragic and dramatic example could be seen in the neurotoxic effects induced by MPTP, a synthesis by-product found in the synthetic opioid MPPP, which led to irreversible precipitation of Parkinsonism in users exposed to this by-product (Langston 2017).

It is hard to estimate the right dose when newly synthesized substances are explored (Shulgin et al. 1986). On an individual level, risks of adverse effects are typically dose-dependent, but both "set" and "setting" are particularly important when working with substances such as LSD, psilocybin, or DMT that, under unsupportive conditions, carry the risk of eliciting traumatic experiences in the individual, thus presenting potential dangers during the acute phase of the inebriation.

Other complications such as unrealistic behavior can usually be limited within controlled and medically equipped environments. As illustrated by the cases of Crowley, Lilly, and Moore, the dynamics of self-experimentation might go beyond originally set limits that might even endanger the experimenter. Another difficulty can manifest in the development of a hypocritical attitude that can also take the form

of "proselytizing," thereby posing risks to others. A more serious form is the fixation on drug effects that lead to feelings of megalomania, sometimes triggered by certain specific drugs (e.g., cocaine or ketamine), and the dependence-producing substance cocaine led some investigators even to become "enslaved" by them (Crowley [1917] 1973; Ring 1887).

An example for some of these dangers can be found in the "Los Angeles group." These were highly qualified psychotherapists who began their therapeutic use of LSD and SEs in the late 1950s. In 1957, Sidney Cohen (of the Los Angeles Neuropsychiatric Institute) ordered LSD for the purpose of legitimate scientific experimentation. However, some of his associates became quite fascinated by the drug's effects and began to experiment on themselves on weekends. By this time, a chain of enthusiastic discovery extended from one researcher to another, which changed the group dynamics to a stage where drug taking itself became the center of attention. As a safety measure, these researchers developed a "buddy system" by which one partner took LSD while the other, abstaining, watched his performance and somewhat guided the experience. The increasing enthusiasm soon extended to include other substances and the establishment of "LSD social parties." Ultimately, the therapists' LSD supplies were confiscated in 1962 (Novak 1997; Caldwell 1968, pp. 47–49).

8 Conclusions

8.1 What Can Be Learned from the History of Self-Experimentation?

A synoptic view on the history of SEs with psychoactive substances leads to the recognition that the pleasures and risks associated with experiencing adverse effects differ regarding context and substances used. For example, it seems that the hallucinogens did not lead to immediate adverse effects when taken under controlled conditions, and they also did not induce behavior associated with dependence. The experiences induced by them have reportedly led to a deeper understanding of patients with psychotic illnesses and neurotic patients within the confines of LSD-assisted psychotherapy. With the recently upcoming new therapeutic methods for the effective treatment of post-traumatic stress disorder (PTSD) by MDMA-assisted psychotherapy (Mithoefer et al. 2011, 2013, 2018) and the use LSD in anxiety disorders (Gasser et al. 2014) and of psilocybin for depression (Carhart-Harris et al. 2016), one might even see a revival of SEs as an important requirement for training therapists who employ these methods.

Under certain circumstances, as seen with some studies and SEs in the past, it may appear that there was no alternative available when exploring new terrain in order to avoid posing risk to others. A notable example is Alexander Shulgin who was possibly one of the greatest self-experimenters and who remained lucid and healthy after nearly 50 years of such research. Even with this case in mind, the risks should not be underestimated and have to be evaluated for every substance in its own

right. This might be particularly relevant today in the world of NPS that might pose high risks to people who use these substances given that toxicological data are commonly unavailable.

Psychologists like William James and Sigmund Freud or philosophers like Benjamin P. Blood have been inspired significantly by their SEs. However, others have been confronted with serious dangers when their self-experimentation got out of control, especially so with substances with more simple and reliable euphoric effects that also carry a higher dependence liability. With such substances, the specific properties of the substances have to be considered in advance. For example, is it more a reliable euphoria-inducing stimulant or is it having unpleasant side effects? What do the animal experiments show in this respect? Does the substance induce "consciousness-expanding" qualities that elicit more intense and complex feelings and thoughts than usual that go beyond the users' usual frame of reference? If this is the case, then documented self-experimenters have tended to shy away from experiencing drug effects under crude and less favorable circumstances. This differs from other drugs such as cocaine, which tend to induce a "simple but reliable state of euphoria," ego-strengthening, and anxiolysis (cf. Table 1). Substances such as cocaine or certain amphetamine-like stimulants, which primarily engage the "reward systems" of the brain, might carry particular health risks through repeated use and/or dependence liability. It can be assumed that goals of self-experimentation serving other functions, such as escapism, manipulation, or psychological coping, are rarely communicated. One exception is the retrospective account of John C. Lilly's ketamine dependence, which began as a SE (Lilly 1978).

Another important aspect is the psychological state of the experimenter. Not all motives are known consciously or in advance. For example, a need for compensating for psychological deficits will predict a preference for substances with properties that allow for such compensation to take place, e.g., euphoric stimulants to cope with depressive feelings; opiates to cope with hyperarousal, depression, and nightmares; and benzodiazepines to cope with anxiety. In contrast, substances with more "complex" or even "consciousness-expanding" effects are not particularly usable for the purpose of coping with psychiatric symptoms. Instead of suppressing psychiatric symptoms or compensating psychological deficits, these substances tend to confront the drug takers with their deficits instead of aiding suppression or compensation.

If SEs appear unavoidable or necessary, it is advantageous for a researcher (or therapist) to work in the framework of controlled SEs where environmental circumstances are carefully controlled and characteristics of the substance used (as well as sufficient toxicological information) are known. These SEs can provide sufficient safety and a more reliable outcome, documentation, and instruction (if used by future researchers or therapists). In contrast, uncontrolled SEs might provide less scientific value and have repeatedly led to "unconventional behavior," social withdrawal, and autistic individual or group behavior. A positive example of serious and safe self-experimentation could be seen in the Swiss Physicians Society for Psycholytic Therapy (SÄPT). In its professional framework, more than 50 physicians have self-experimented under orderly and safe conditions for more than 30 years and did not produce any adverse effects (Gasser 2017, Personal

communication, Styk 1994). Other examples of safely controlled SEs were those conducted in clinical treatment centers where LSD therapy was practiced, which never resulted in grave complications (e.g., Winkler and Csémy 2014).

In summary, it appears that self-experimentation with psychoactive substances has, besides a continuous history for over 125 years, stimulated scientific (and therapeutic) advances. However, examples also exist that might serve as cautionary tales involving a variety of potentially dangerous dynamics, be it on an individual or group level.

As recent scientific and ethical restrictions do not allow for much scientifically driven SEs anymore, one can assume that the great times of undertaking controlled SEs appear to be over. Safely controlled SEs might find their legitimate place in the future in the training of therapists and the education of experimental researchers. As the last 15 years have shown, the future might see a further expansion of the spectrum and range of NPS and "self-experimentation" with them by curious laypersons, "para-professional" experimenters, or users with drug dependence. This type of drug taking might not be influenced by existing legislative control. During the last 10 years, it has consistently been argued that attempts to prohibit most psychoactive substances have led to the emergence of "new," and sometimes more harmful, successors. The easily foreseeable (and probably chaotic and dangerous) experimentation with NPS of the future might be restricted to the "wild" category performed by nonscientists, thus limiting safety and gains in scientific knowledge. With this in mind, it appears even more important what Altman (1972, p. 351) has concluded in his study on medical self-experimentation: ". . . The mere act of doing the experiment on oneself justifies neither a poorly designed experiment nor the same well designed experiment on someone else" (Altman 1972, p. 351).

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