Chapter 1

Introduction

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Drugs that are used for purposes other than medical treatment have been a part of the sociocultural landscape since antiquity and the crossing over of drugs between recreational use, ritual and cultural use, and medical treatment can also be demonstrated with examples throughout history. Indeed, many ancient and traditional belief systems perform rituals that include psychoactive drugs as an integral part of treatment. In more modern times pharmacotherapy has become increasingly organized and regulated, and recreational drugs criminalized and excluded from the clinical setting. A dichotomy has developed between recreational drugs and medical pharmacotherapies that is being challenged by emerging evidence and clinical use.

Interestingly, the exclusion of drugs now labeled "recreational" or "illicit" has a relatively short history. Cocaine was used legally by Sigmund Freud as a treatment for melancholia and became a widely used treatment until the 1930s when it fell out of favor due to its potential for addiction and abuse. Freud himself stopped treating patients with cocaine in 1887 after recommending it to treat morphine addiction in a colleague and friend, Ernst von Fleischl-Marxow, who developed "cocaine psychosis" and died a few years later [1]. Early prohibition laws focused initially on alcohol and later on pharmaceuticals. These were reactive to a perceived social or moral problem. Cocaine and morphine were restricted in the United States from 1914, available only with a prescription. Criminalization of cannabis has an extensive and circuitous history that accelerated with the formation of the US Federal Bureau of Narcotics in 1930.

With criminalization, stigmatization and misinformation also became features of cultural attitudes toward nonprescription drug use, as well as the association of drug use with counterculture, jazz music, beat poets, and later nonconformist groups. Nevertheless, when Dr. Timothy Leary experimented with lysergic acid diethylamide (LSD) and psilocybin at Harvard University in the 1960s, he did so legally. Leary was fired from Harvard as he was advocating use of psychedelics among his students and peers, not because of the research that he conducted such as the Concord Prison Experiment. Indeed, many of his contemporaries were trialing LSD and psilocybin as treatments for psychiatric disorders, with LSD estimated to have been given to approximately 40,000 human research subjects by 1963 [2]. Of note, much of the early research with psychedelics was conducted within the US military by researchers who were very conservative and certainly not associated with counterculture in experiments that aimed to uncover pharmacological strategies that could be deployed during interrogation. Research and access became increasingly more restricted, ending definitively with the introduction of the Controlled Substances Act in 1970 and coinciding with the "War on Drugs," a global effort led by the United States to eradicate illicit drugs using strategies such as greatly increased penalties, enforcement, and incarceration.

Recently, there has been an easing of some of the laws restricting recreational drug use, and with these changes new opportunities have emerged for further research and treatment using drugs that were previously heavily restricted. Undoubtably, the key driver of the changing legal landscape has been the dismal failure of the War on Drugs, which is continuing to cause harm through the criminalization of drug users and the emergence of powerful, wealthy, and violent organized crime groups that have grown and profited from a legal framework that attracts the most nefarious elements of society. This has also occurred in the context of a thinning treatment discovery pipeline, notwithstanding great commercial investment, and the renewed enthusiasm for exploration of recreational drugs by key research and public figures.

Decriminalization of recreational drug use is an evolving reform that prevents drug users with no

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other criminal involvement from being caught up in the justice system. The relaxation of laws restricting recreational drugs has also created an environment where repurposing recreational drugs for medical use has become possible, with new legal frameworks, regulatory approvals, drug formulations, and guidelines permitting previously illicit drugs to fit into a modern medical environment.

The imperfections of the War on Drugs have sparked reconsideration of drug laws; however, from various directions strong pressure for further reforms is being applied to politicians and other stakeholders. Pressure is coming from patients and their supporters with untreated or inadequately treated illnesses who are hoping for new breakthrough treatments. Elsewhere, some advocates for legalization of recreational drugs see medical use as a step toward achieving their business and social goals. Moreover, industry representatives see new business opportunities in areas such as cannabis production and pharmaceutical formulation and production of repurposed recreational drugs. Legal medicinal and recreational cannabis is currently a $21 billion industry and growing. However, pressure is also coming from researchers motivated by knowledge discovery and clinicians motivated by improving patient outcomes, who are engaged in evidence-based research and are convinced by the potential of the field and from patients who have already benefited from treatment.

This book has been written by researchers and academics chosen for their experience and expert knowledge. Specifically, chapter authors are experts and experienced researchers in the drugs profiled in their chapter. In this book, we cover the pharmacology of selected drugs and discuss the controversies and politics of the repurposing of recreational drugs as medical therapies with sufficient detail for the reader to appreciate the complexity of this issue and the range of views. The authors aim to take a balanced and careful approach, avoiding advocacy for either side of the drug debate and adhering to the scientific position of requiring the debate to be driven by evidence. Where known, the mechanisms of action, pharmacokinetics, putative indication, and safety and tolerability will be described for each agent.

Even among academics, views vary, especially where evidence and high-quality, large research studies are scarce. Some academics may show skepticism for repurposing of recreational drugs, emphasizing known risks and methodological shortcomings, whereas others may be fully supportive, emphasizing the promise of the field, even though they are both basing their views on the same evidence. Indeed, some academics may be supportive of the repurposing of one class of recreational drug and skeptical of another. All academics reach their conclusions about the clinical utility of a drug by balancing the benefits of treatment with the risks; however, benefits and risks can be evaluated differently, especially when evidence is limited, as is the case currently. The editors of this book have decided that for each chapter, the views and perspectives of the authors as submitted in their chapters for this volume must be preserved in the final version of the edited book. Chapter authors were invited for their leadership and expertise, not necessarily because their views parallel those of the editors. Chapter authors were given complete liberty concerning what to cover in their chapter, apart from being asked to include the pharmacology of the drug they were writing about. The only other instructions to chapter authors were in regard to word length and format. We are delighted that the book contains a plurality of voices.

Nevertheless, when someone is a pioneer of and expert in a specific treatment, they are generally favorable toward that treatment. Some readers may feel that there is a lack of opposing voices in this book, that recreational drugs cause harm, and that the book should include at least one voice to emphasize that point. We believe that point is adequately mentioned here in the introduction and in Chapter 2, which discusses ethical considerations. Other readers may feel that this book doesn't go far enough and is a missed opportunity to advocate for drug reforms. In reply, we would argue that this is a scientific text intended to be read by people in the scientific, medical, or health care community where people generally hold varied but nuanced views, rather than condemnation or advocacy of emerging treatments. This book focuses on evidence.

Selected Recreational Drugs

There are several methodological issues that complicate the field. Recreational drugs are not consistently defined. Non-medical use of drugs can include performance-enhancing drugs in sport and ritual or traditional use of drugs. Cannabis can be used as a recreational drug and is also used traditionally in some religious practices, such as in Hinduism in association with the god Shiva. This suggests that the

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category of recreational drugs may be better described by the purpose for which the drug is used, but this is also problematic as caffeine, nicotine, and alcohol are not usually described as recreational drugs. Illicit status is also not helpful when defining recreational drugs as laws change, whereas the pharmacology of drugs doesn't change. Consumption of illicit drugs as self-medication for a medical problem also confounds the definition of recreational drugs. Nevertheless, when discussing recreational drugs there is broad consensus around which drugs are included. Recreational drugs are defined by their social status and use, not by their pharmacology; however, they generally are psychoactive and may be associated with abuse or addiction.

A list of all recreational drugs would be a long one that would include many drugs with similar mechanisms of action and drug effects and many uncommon drugs known only in specific communities or geographic regions. There is no comprehensive list, but such a list would include over 100 different drugs. Even a list of common recreational drugs would include approximately 20 drugs.

Recreational drugs have been selected for inclusion in this book because there are established research groups supported by their universities and/or industry partners that are actively investigating drug repurposing as medical treatments. Recreational drugs that, at the time of writing this book, have already received regulatory approval for medical use in some states or countries have been prioritized for inclusion in this book. Chapter authors have been invited to contribute to this book because of their expertise and international recognition as leaders of research investigating the drug described in their chapter.

We accept that there are recreational drugs that have not received a dedicated chapter in this book that may be considered for future repurposing for medical treatment. For some drugs, the evidence for medical use is very limited or contradictory, or there is evidence that harm outweighs benefit. Some drugs do not merit inclusion, and there are examples of agents that are on the margins of the definition, such as drugs like kava for generalized anxiety disorder, that fell below the line and could have deserved greater mention. Mambé, or chewed coca leaves that may be mixed with other substances, as well as kambo from the frog *Phyllomedusa bicolor* and other substances used in traditional medicine and ritual are not included as chapters in this book. Their traditional use does not point to treatment for recognized medical conditions and claims of treatment efficacy by alternative therapy practitioners have not been substantiated. In the case of kambo, harm, including fatal outcomes, has been documented.

Alternative medicine claims of benefit of treatment as "wellness" or "detox" are considered pseudoscientific by the medical establishment and debate on this topic is outside the scope of this book. With future research, some drugs that currently have limited evidence may emerge as useful treatments. Similarly, future research may find that some drugs that are not beneficial when consumed in their recreational formulation may be beneficial or safer when reformulated or have beneficial synthetic analogs. Of course, a limitation of all books is that the information they contain may become dated. The authors have attempted to address this by focusing on pharmacology. In particular, the regulatory environment for recreational drugs is rapidly changing and comments on laws and regulations are only accurate at the time of publication.

Different Ways in Which Recreational Drugs Can Become Medical Treatments

There are well-established pathways that the conventional pharmaceutical industry uses to develop a new product and bring it to market as a new treatment. Regulatory authorities expect processes to be followed and carefully check for compliance. Medical practitioners are reliant on established processes and the vigilance of regulatory authorities so that they can be confident that the treatments they are prescribing are evidence based, effective, and safe. Conventional regulatory pathways also provide medical practitioners with important information to assist them with clinical decision-making, such as indications, contraindications, dosing recommendations, adverse effects, and drug interaction risks. The repurposing of recreational drugs as medical treatments does not follow conventional pathways for regulatory approval and important clinical information may be limited.

The illicit status of recreational drugs has delayed or prevented research required by conventional pharmaceuticals for regulatory purposes and registration. In many cases, necessary preclinical research to determine the pharmacodynamic and pharmacokinetic properties of the drug was illegal for several decades

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and is still subject to tight legal regulations. Furthermore, there is still stigma associated with their use. Consequently, there exists a paucity of preclinical data for some drugs and clinical trials are often conducted with small budgets and small sample sizes. Data quality often doesn't reach the standard asked by regulatory authorities from the pharmaceutical industry when registering a new product.

To become a medical treatment, recreational drugs will usually need to be approved by a regulatory body. A submission for drug approval made to the regulatory body must comply with the requirements of the regulatory body. Legalization of medicinal cannabis in California was achieved when Proposition 215, the Compassionate Use Act of 1996 [3], was voted into law, bypassing the usual processes of the US Food and Drug Administration (FDA). Legalization of psilocybin and methylenedioxymethamphetamine (MDMA) for medical use in Australia in 2023 was achieved when the regulatory body, the Therapeutic Goods Administration (TGA), reclassified the two substances from a schedule 9 to a schedule 8 listing, in response to over 6,000 public submissions and an expert report [4]. Approval processes that are non-conventional are controversial and may be subject to legal challenge, as was the case with Proposition 215, which was challenged in the US Supreme Court. Achieving legalization through court processes can lead to anomalies, such as with Proposition 215 that legalized medicinal cannabis without removing the restrictions on medical research using cannabis and without changing federal laws. The Medical Marijuana Regulation and Safety Act was not passed in California until 2015. Approval processes for each recreational drug repurposed for medical use are considered on a case-by-case basis and may vary between drugs.

Effective Treatments in Their Own Right

Some recreational drugs have been repurposed as medical treatments where treatment efficacy was suggested directly from experiences of recreational drug users. Medicinal cannabis is an example of this, where self-medication for underlying medical conditions was widely reported. Not only has medicinal cannabis not followed conventional pathways for drug development and registration, but the establishment of the medicinal cannabis industry has often been activist led. The role of "activists" is discussed in further detail in the sub-section "Translating Research into Clinical Practice," below. Nevertheless, the pharmaceutical industry has developed formulations of cannabinoids that have often been welcomed by treating clinicians who prefer to follow official dosage guidelines rather than the *ad libitum* consumption observed with self-medication.

The antidepressive properties of ketamine are also an example of a recreational drug that is an effective treatment. Ketamine has a long history of medical and veterinary use as an anesthetic and analgesic, which has facilitated its repurposing as an antidepressant. It differs from almost all other agents covered in this book, in that it has existing regulatory approval as an anesthetic agent, greatly facilitating translation and implementation.

Where a recreational drug is shown to be an effective treatment for a mental health indication, there are still considerations regarding dosing, formulation and safety that need to be addressed through research.

Traditional and Alternative Treatments

Psychedelic drugs have been used by some Indigenous communities in rituals and traditional medicine. Treatment has often had mystical or spiritual goals congruent with the belief systems of the Indigenous groups. Use by alternative therapy practitioners may aim for mystical experiences as treatment goals or those practitioners have made claims of benefits of treatment without providing evidence. More recently, clinical trials have been conducted in reputable universities; however, approval of psilocybin and MDMA for clinical treatment has been driven by activist campaigns.

Arguably, to traditional Indigenous groups and to alternative medicine practitioners, the need to demonstrate that treatments are efficacious for illnesses that are recognized by conventional medical practitioners may not be something that they consider necessary, or even of any value at all. Similarly, patients who engage in traditional or alternative therapies may be attracted to the spiritual or mystical goals of the practitioner. Balancing benefit with harm may be complicated.

Pharmacophores and Analogs

Herbal and biological treatments that are psychoactive may be investigated as treatments in their natural state or modified in the laboratory. A pharmacophore is, in this case, the part of the molecule that binds or interacts

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with pharmacological targets in the human brain. By knowing the chemical structure of a pharmacophore, researchers in a laboratory may be able to develop new chemical entities that share or have similar effects to the psychoactive properties of the original, naturally occurring psychoactive substance. These new chemical entities may have advantages over the original treatment, such as different pharmacodynamic and pharmacokinetic parameters, different safety parameters, and benefits for production and standardization.

Chapter 9, "From Betel Nuts to Cobenfy," gives an example of a drug analog being developed for clinical use that has its origin in a recreational drug. The antipsychotic xanomeline is an example and is an analog of arecoline, the main pharmacologically active biochemical in betel nut.

The Importance of the Clinical Setting

Translating Research into Clinical Practice

Conventional pharmaceuticals have well-established paths for translation from research into practice, requiring extensive preclinical research prior to any human drug trials. Clinical drugs trials, phases I, II, and III, as well as preclinical data are thoroughly reviewed by regulatory authorities with approval requiring proof of safety and efficacy. Repurposed recreational drugs do not necessarily pass through these pathways and can obtain approval for clinical use through other mechanisms. Each drug is considered on a case-by-case basis and has had various pathways of translation from research to clinical practice. Ketamine, repurposed to treat depression, has had the most conventional pathway, already approved for clinical use for analgesia and anesthesia; approval for treatment-resistant depression required adding an extra indication for use. Some other drugs have had very different pathways to regulatory approval.

Role of Activists

Activists have been prominent, and their demands and legal maneuvers have often spearheaded changes that have opened opportunities for greater research and availability of recreational drugs, repurposed as medical treatments. This is especially the case with medicinal cannabis, but also with psilocybin and MDMA, and will continue to be a prominent driver of further reforms. Activists have diverse objectives, backgrounds, and motivations. Recreational drug users who are pursuant of wide reforms of drug laws may support medical repurposing of recreational drugs, as they can see that recreational drug users may benefit from these reforms. They may also genuinely believe that some recreational drugs have therapeutic value. Activists and commercial interests may also have overlapping goals, although it would be likely that only a minority of activists are primarily motivated by commercial interests. Nevertheless, patient advocacy and commercial interests have greater capacity to lobby politicians and engage lawyers. People who suffer from illnesses that are inadequately managed by conventional therapies, and their families and supporters, who believe that they may benefit from treatment with repurposed recreational drugs, have been prominent activists for legal reforms that will allow them access to these treatments. And individuals and groups may be able to wear multiple hats and choose to use the one that suits a particular purpose.

Activist-led reforms can be controversial. Some examples are the Trojan horse strategy, where pressure for medicinal use of recreational drugs is a mechanism for furthering an agenda of recreational use or overt or covert commercial gain. This strategy has been used at least since Lydia Pinkham's Vegetable Compound was consumed during the period of alcohol prohibition. More recently, a medicinal marijuana card is sought by recreational marijuana users. The actions of activists have broken the barriers that limit access to recreational drugs, and in doing so they are sometimes willing to bypass or challenge the regulatory system that oversees medical treatments. Regulatory bodies, such as the FDA, include in their history a mandate to regulate against products that make false therapeutic claims, a problem that was unregulated in the United States prior to the Sherley Amendment passing the US Congress in 1912 [5]. Understandably, the medical establishment is resistant to efforts to soften regulatory requirements for new pharmaceuticals, mindful that most proposed new treatments either fail to show expected clinical benefits or demonstrate clinical risks. To the medical establishment, the laws that made recreational drug use illegal and the regulations for the registration of pharmaceutical treatments are very different things. To activists, both may be regarded as barriers. In addition, people from the medical establishment may have concerns about

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the public health consequences of repealing laws that restrict access to recreational drugs.

Furthermore, health professionals and researchers have diverse views on the topic of recreational drug repurposing, ranging from opposition to advocacy, with nuanced views being common. As is often the case in the public arena, the smaller number of voices at the extremes are generally louder than the large number in the center. Activist views from within the medical profession also exist. To researchers, it is evidence that drives progress, but with the involvement of activism the lines between what levels of evidence are required become blurred and the boundary between recreational and medical use becomes less distinct. Neatly dichotomizing recreational and medical use of drugs may be fanciful. Nevertheless, for researchers an awareness of the requirements and standards expected for a medical treatment is essential.

Mainstream Views

Use of recreational drugs remains highly stigmatized in the general public, due to perceived harms and their association with subcultures and criminal activity. Yet elsewhere, media reports have referred to repurposed recreational drugs using terms such as "breakthroughs," "wonder drugs," and "miracle medicine." Patients, especially those who have responded inadequately to conventional therapies, will often have a hopeful view toward controversial treatments. In addition, patient acceptance of novel therapies may be influenced by the therapeutic alliance they have with their treating clinician. Diversity of views is considerable in the broader community and influences such as upbringing, views of peers, and personal experiences will also affect views held by individuals.

Attitudes of Researchers, Academics, and Clinicians

Scientists are trained to be skeptical, approving new advances in treatment when convinced by the evidence. In theory, scientist should be impartial if a new treatment has an illicit history and look only at the evidence. In practice, scientists are subject to the same influences as the broader community and have often been slow to accept change. With the repurposing of recreational drugs, a broad range of views is apparent in the scientific community. These views are facilitated by evidence that is not overwhelming, negative studies, adverse effects, and people holding supportive views for some repurposed drugs and opposing views for others. With the regulatory approval of some of these drugs, the views of key opinion leaders and unpublished clinical experience can be decisive in firming opinions. Clinical experience can be reaffirming, observing patients who respond who had previously been non-responsive to conventional treatments, or repudiating through non-response, adverse effects, or experience with prescription-seeking recreational drug users.

This book includes views and opinions that are controversial and that many people will disagree with. However, the chapter authors are experts in their fields and their views are based on their interpretation of peer-reviewed evidence. This book faithfully presents their work.

Objectives

The objectives of this book are the following:

- Identify recreational or traditional drugs being repurposed as new pharmacotherapies
- Investigate the evidence base to support the therapeutic use for these drugs, including harms and benefits, and to detail clinical use
- Understand the complex pharmacology of these drugs
- Understand the limits in the knowledge base around these drugs
- Understand why these drugs are controversial and the changing political and social environment

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