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Chemoinformatics and Computational Chemistry in Drug Studies

Dr. Ashutosh Tripathi

Associate Professor, Dept. of Chemistry, KS Saket PG College, Ayodhya, Uttar Pradesh, India

ABSTRACT: Cheminformatics (also known as **chemoinformatics**) refers to the use of physical chemistry theory with computer and information science techniques—so called "*in silico*" techniques—in application to a range of descriptive and prescriptive problems in the field of chemistry, including in its applications to biology and related molecular fields. Such *in silico* techniques are used, for example, by pharmaceutical companies and in academic settings to aid and inform the process of drug discovery, for instance in the design of well-defined combinatorial libraries of synthetic compounds, or to assist in structure-based drug design. The methods can also be used in chemical and allied industries, and such fields as environmental science and pharmacology, where chemical processes are involved or studied.

KEYWORDS- chemoinformatics, chemistry, drug, pharmacology, technology

I. INTRODUCTION

Cheminformatics has been an active field in various guises since the 1970s and earlier, with activity in academic departments and commercial pharmaceutical research and development departments.[2][The term chemoinformatics was defined in its application to drug discovery by F.K. Brown in 1998:[3]

Chemoinformatics is the mixing of those information resources to transform data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and optimization.

Since then, both terms, cheminformatics and chemoinformatics, have been used.although, lexicographically, cheminformatics appears to be more frequently used,[despite academics in Europe declaring for the variant chemoinformatics in 2006.[6] In 2009, a prominent Springer journal in the field was founded by transatlantic executive editors named the Journal of Cheminformatics.[7]

Background

Cheminformatics combines the scientific working fields of chemistry, computer science, and information science—for example in the areas of topology, chemical graph theory, information retrieval and data mining in the chemical space.[8][Cheminformatics can also be applied to data analysis for various industries like paper and pulp, dyes and such allied industries.[12]

Applications

Storage and retrieval

A primary application of cheminformatics is the storage, indexing, and search of information relating to chemical compounds. The efficient search of such stored information includes topics that are dealt with in computer science, such as data mining, information retrieval, information extraction, and machine learning. Related research topics include:

- Digital libraries
- Unstructured data
- Structured data mining and mining of structured data
  - Database mining
  - Graph mining

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- Molecule mining
- Sequence mining
- Tree mining

File formats

The *in silico* representation of chemical structures uses specialized formats such as the Simplified molecular input line entry specifications (SMILES)[13] or the XML-based Chemical Markup Language.[14] These representations are often used for storage in large chemical databases. While some formats are suited for visual representations in two- or three-dimensions, others are more suited for studying physical interactions, modeling and docking studies.

Virtual libraries

Chemical data can pertain to real or virtual molecules. Virtual libraries of compounds may be generated in various ways to explore chemical space and hypothesize novel compounds with desired properties. Virtual libraries of classes of compounds (drugs, natural products, diversity-oriented synthetic products) were recently generated using the FOG (fragment optimized growth) algorithm.[15] This was done by using cheminformatic tools to train transition probabilities of a Markov chain on authentic classes of compounds, and then using the Markov chain to generate novel compounds that were similar to the training database.

Virtual screening

In contrast to high-throughput screening, virtual screening involves computationally screening *in silico* libraries of compounds, by means of various methods such as docking, to identify members likely to possess desired properties such as biological activity against a given target. In some cases, combinatorial chemistry is used in the development of the library to increase the efficiency in mining the chemical space. More commonly, a diverse library of small molecules or natural products is screened.

Quantitative structure-activity relationship (QSAR)

This is the calculation of quantitative structure–activity relationship and quantitative structure property relationship values, used to predict the activity of compounds from their structures. In this context there is also a strong relationship to chemometrics. Chemical expert systems are also relevant, since they represent parts of chemical knowledge as an *in silico* representation. There is a relatively new concept of matched molecular pair analysis or prediction-driven MMPA which is coupled with QSAR model in order to identify activity cliff.[16]

II. DISCUSSION

Computational chemistry is a branch of chemistry that uses computer simulation to assist in solving chemical problems. It uses methods of theoretical chemistry, incorporated into computer programs, to calculate the structures and properties of molecules, groups of molecules, and solids. It is essential because, apart from relatively recent results concerning the hydrogen molecular ion (dihydrogen cation, see references therein for more details), the quantum many-body problem cannot be solved analytically, much less in closed form. While computational results normally complement the information obtained by chemical experiments, it can in some cases predict hitherto unobserved chemical phenomena. It is widely used in the design of new drugs and materials.[1]

Examples of such properties are structure (i.e., the expected positions of the constituent atoms), absolute and relative (interaction) energies, electronic charge density distributions, dipoles and higher multipole moments, vibrational frequencies, reactivity, or other spectroscopic quantities, and cross sections for collision with other particles.

The methods used cover both static and dynamic situations. In all cases, the computer time and other resources (such as memory and disk space) increase quickly with the size of the system being studied. That system can be a molecule, a group of molecules, or a solid. Computational chemistry methods range from very approximate to highly accurate; the latter is usually feasible for small systems only. *Ab initio* methods are based entirely on quantum mechanics and basic physical constants. Other methods are called empirical or semi-empirical because they use additional empirical parameters.

Both *ab initio* and semi-empirical approaches involve approximations. These range from simplified forms of the first-principles equations that are easier or faster to solve, to approximations limiting the size of the system (for example, periodic boundary conditions), to fundamental approximations to the underlying equations that are required to achieve any solution to them at all. For example, most *ab initio* calculations make the Born–Oppenheimer approximation, which greatly simplifies the underlying Schrödinger equation by assuming that the nuclei remain in

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place during the calculation. In principle, *ab initio* methods eventually converge to the exact solution of the underlying equations as the number of approximations is reduced. In practice, however, it is impossible to eliminate all approximations, and residual error inevitably remains. The goal of computational chemistry is to minimize this residual error while keeping the calculations tractable.

In some cases, the details of electronic structure are less important than the long-time phase space behavior of molecules. This is the case in conformational studies of proteins and protein-ligand binding thermodynamics. Classical approximations to the potential energy surface are used, typically with molecular mechanics force fields, as they are computationally less intensive than electronic calculations, to enable longer simulations of molecular dynamics. Furthermore, cheminformatics uses even more empirical (and computationally cheaper) methods like machine learning based on physicochemical properties. One typical problem in cheminformatics is to predict the binding affinity of drug molecules to a given target. Other problems include predicting binding specificity, off-target effects, toxicity, and pharmacokinetic properties.

Building on the founding discoveries and theories in the history of quantum mechanics, the first theoretical calculations in chemistry were those of Walter Heitler and Fritz London in 1927, using valence bond theory. The books that were influential in the early development of computational quantum chemistry include Linus Pauling and E. Bright Wilson's 1935 *Introduction to Quantum Mechanics – with Applications to Chemistry*, Eyring, Walter and Kimball's 1944 *Quantum Chemistry*, Heitler's 1945 *Elementary Wave Mechanics – with Applications to Quantum Chemistry*, and later Coulson's 1952 textbook *Valence*, each of which served as primary references for chemists in the decades to follow.

With the development of efficient computer technology in the 1940s, the solutions of elaborate wave equations for complex atomic systems began to be a realizable objective. In the early 1950s, the first semi-empirical atomic orbital calculations were performed. Theoretical chemists became extensive users of the early digital computers. One major advance came with the 1951 paper in Reviews of Modern Physics by Clemens C. J. Roothaan in 1951, largely on the "LCAO MO" approach (Linear Combination of Atomic Orbitals Molecular Orbitals), for many years the second-most cited paper in that journal. A very detailed account of such use in the United Kingdom is given by Smith and Sutcliffe.[2] The first *ab initio* Hartree–Fock method calculations on diatomic molecules were performed in 1956 at MIT, using a basis set of Slater orbitals. For diatomic molecules, a systematic study using a minimum basis set and the first calculation with a larger basis set were published by Ransil and Nesbet respectively in 1960.[3] The first polyatomic calculations using Gaussian orbitals were performed in the late 1950s. The first configuration interaction calculations were performed in Cambridge on the EDSAC computer in the 1950s using Gaussian orbitals by Boys and coworkers.[4] By 1971, when a bibliography of *ab initio* calculations was published,[5] the largest molecules included were naphthalene and azulene.[6][7] Abstracts of many earlier developments in *ab initio* theory have been published by Schaefer.[8]

In 1964, Hückel method calculations (using a simple linear combination of atomic orbitals (LCAO) method to determine electron energies of molecular orbitals of π electrons in conjugated hydrocarbon systems) of molecules, ranging in complexity from butadiene and benzene to ovalene, were generated on computers at Berkeley and Oxford.[9] These empirical methods were replaced in the 1960s by semi-empirical methods such as CNDO.[10]

In the early 1970s, efficient *ab initio* computer programs such as ATMOL, Gaussian, IBMOL, and POLYAYTOM, began to be used to speed *ab initio* calculations of molecular orbitals. Of these four programs, only Gaussian, now vastly expanded, is still in use, but many other programs are now in use. At the same time, the methods of molecular mechanics, such as MM2 force field, were developed, primarily by Norman Allinger.[11]

One of the first mentions of the term *computational chemistry* can be found in the 1970 book *Computers and Their Role in the Physical Sciences* by Sidney Fernbach and Abraham Haskell Taub, where they state "It seems, therefore, that 'computational chemistry' can finally be more and more of a reality."[12] During the 1970s, widely different methods began to be seen as part of a new emerging discipline of *computational chemistry*.[13] The *Journal of Computational Chemistry* was first published in 1980.

Computational chemistry has featured in several Nobel Prize awards, most notably in 1998 and 2013. Walter Kohn, "for his development of the density-functional theory", and John Pople, "for his development of computational methods in quantum chemistry", received the 1998 Nobel Prize in Chemistry.[14] Martin Karplus, Michael Levitt and Arieh Warshel received the 2013 Nobel Prize in Chemistry for "the development of multiscale models for complex chemical systems".[15]

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Fields of application

The term *theoretical chemistry* may be defined as a mathematical description of chemistry, whereas *computational chemistry* is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. In theoretical chemistry, chemists, physicists, and mathematicians develop algorithms and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions.

Computational chemistry has two different aspects:

- Computational studies, used to find a starting point for a laboratory synthesis or to assist in understanding experimental data, such as the position and source of spectroscopic peaks.
- Computational studies, used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms not readily studied via experiments.

Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects.

Several major areas may be distinguished within computational chemistry:

- The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied.[16]
- Storing and searching for data on chemical entities (see chemical databases).
- Identifying correlations between chemical structures and properties (see *quantitative structure–property relationship* (QSPR) and *quantitative structure–activity relationship* (QSAR)).
- Computational approaches to help in the efficient synthesis of compounds.
- Computational approaches to design molecules that interact in specific ways with other molecules (e.g. drug design and catalysis).

Accuracy

Computational chemistry is not an *exact* description of real-life chemistry, as our mathematical models of the physical laws of nature can only provide us with an approximation. However, the majority of chemical phenomena can be described to a certain degree in a qualitative or approximate quantitative computational scheme.

Molecules consist of nuclei and electrons, so the methods of quantum mechanics apply. Computational chemists often attempt to solve the non-relativistic Schrödinger equation, with relativistic corrections added, although some progress has been made in solving the fully relativistic Dirac equation. In principle, it is possible to solve the Schrödinger equation in either its time-dependent or time-independent form, as appropriate for the problem in hand; in practice, this is not possible except for very small systems. Therefore, a great number of approximate methods strive to achieve the best trade-off between accuracy and computational cost.

Accuracy can always be improved with greater computational cost. Significant errors can present themselves in ab initio models comprising many electrons, due to the computational cost of full relativistic-inclusive methods. This complicates the study of molecules interacting with high atomic mass unit atoms, such as transitional metals and their catalytic properties. Present algorithms in computational chemistry can routinely calculate the properties of small molecules that contain up to about 40 electrons with errors for energies less than a few kJ/mol. For geometries, bond lengths can be predicted within a few picometers and bond angles within 0.5 degrees. The treatment of larger molecules that contain a few dozen atoms is computationally tractable by more approximate methods such as density functional theory (DFT).

There is some dispute within the field whether or not the latter methods are sufficient to describe complex chemical reactions, such as those in biochemistry. Large molecules can be studied by semi-empirical approximate methods. Even larger molecules are treated by classical mechanics methods that use what are called molecular mechanics (MM). In QM-MM methods, small parts of large complexes are treated quantum mechanically (QM), and the remainder is treated approximately (MM).

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One molecular formula can represent more than one molecular isomer: a set of isomers. Each isomer is a local minimum on the energy surface (called the potential energy surface) created from the total energy (i.e., the electronic energy, plus the repulsion energy between the nuclei) as a function of the coordinates of all the nuclei. A stationary point is a geometry such that the derivative of the energy with respect to all displacements of the nuclei is zero. A local (energy) minimum is a stationary point where all such displacements lead to an increase in energy. The local minimum that is lowest is called the global minimum and corresponds to the most stable isomer. If there is one particular coordinate change that leads to a decrease in the total energy in both directions, the stationary point is a transition structure and the coordinate is the reaction coordinate. This process of determining stationary points is called geometry optimization.

The determination of molecular structure by geometry optimization became routine only after efficient methods for calculating the first derivatives of the energy with respect to all atomic coordinates became available. Evaluation of the related second derivatives allows the prediction of vibrational frequencies if harmonic motion is estimated. More importantly, it allows for the characterization of stationary points. The frequencies are related to the eigenvalues of the Hessian matrix, which contains second derivatives. If the eigenvalues are all positive, then the frequencies are all real and the stationary point is a local minimum. If one eigenvalue is negative (i.e., an imaginary frequency), then the stationary point is a transition structure. If more than one eigenvalue is negative, then the stationary point is a more complex one and is usually of little interest. When one of these is found, it is necessary to move the search away from it if the experimenter is looking solely for local minima and transition structures.

The total energy is determined by approximate solutions of the time-dependent Schrödinger equation, usually with no relativistic terms included, and by making use of the Born–Oppenheimer approximation, which allows for the separation of electronic and nuclear motions, thereby simplifying the Schrödinger equation. This leads to the evaluation of the total energy as a sum of the electronic energy at fixed nuclei positions and the repulsion energy of the nuclei. A notable exception is certain approaches called direct quantum chemistry, which treat electrons and nuclei on a common footing. Density functional methods and semi-empirical methods are variants of the major theme. For very large systems, the relative total energies can be compared using molecular mechanics. The ways of determining the total energy to predict molecular structures are:

Ab initio methods

The programs used in computational chemistry are based on many different quantum-chemical methods that solve the molecular Schrödinger equation associated with the molecular Hamiltonian. Methods that do not include any empirical or semi-empirical parameters in their equations – being derived directly from theoretical principles, with no inclusion of experimental data – are called *ab initio methods*. This does not imply that the solution is an exact one; they are all approximate quantum mechanical calculations. It means that a particular approximation is rigorously defined on first principles (quantum theory) and then solved within an error margin that is qualitatively known beforehand. If numerical iterative methods must be used, the aim is to iterate until full machine accuracy is obtained (the best that is possible with a finite word length on the computer, and within the mathematical and/or physical approximations made).

The simplest type of *ab initio* electronic structure calculation is the Hartree–Fock method (HF), an extension of molecular orbital theory, in which the correlated electron-electron repulsion is not specifically taken into account; only its average effect is included in the calculation. As the basis set size is increased, the energy and wave function tend towards a limit called the Hartree–Fock limit. Many types of calculations (termed post-Hartree–Fock methods) begin with a Hartree–Fock calculation and subsequently correct for electron-electron repulsion, referred to also as electronic correlation. As these methods are pushed to the limit, they approach the exact solution of the non-relativistic Schrödinger equation. To obtain exact agreement with the experiment, it is necessary to include relativistic and spin orbit terms, both of which are far more important for heavy atoms. In all of these approaches, along with a choice of method, it is necessary to choose a basis set. This is a set of functions, usually centered on the different atoms in the molecule, which are used to expand the molecular orbitals with the linear combination of atomic orbitals (LCAO) molecular orbital method ansatz. Ab initio methods need to define a level of theory (the method) and a basis set.

The Hartree–Fock wave function is a single configuration or determinant. In some cases, particularly for bond-breaking processes, this is inadequate, and several configurations must be used. Here, the coefficients of the configurations, and of the basis functions, are optimized together.

The total molecular energy can be evaluated as a function of the molecular geometry; in other words, the potential energy surface. Such a surface can be used for reaction dynamics. The stationary points of the surface lead to predictions of different isomers and the transition structures for conversion between isomers, but these can be determined without full knowledge of the complete surface.

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A particularly important objective, called computational thermochemistry, is to calculate thermochemical quantities such as the enthalpy of formation to chemical accuracy. Chemical accuracy is the accuracy required to make realistic chemical predictions and is generally considered to be 1 kcal/mol or 4 kJ/mol. To reach that accuracy in an economic way it is necessary to use a series of post-Hartree–Fock methods and combine the results. These methods are called quantum chemistry composite methods.

Density functional methods

Density functional theory (DFT) methods are often considered to be *ab initio methods* for determining the molecular electronic structure, even though many of the most common functionals use parameters derived from empirical data, or from more complex calculations. In DFT, the total energy is expressed in terms of the total one-electron density rather than the wave function. In this type of calculation, there is an approximate Hamiltonian and an approximate expression for the total electron density. DFT methods can be very accurate for little computational cost. Some methods combine the density functional exchange functional with the Hartree–Fock exchange term and are termed hybrid functional methods.

Semi-empirical methods

Semi-empirical quantum chemistry methods are based on the Hartree–Fock method formalism, but make many approximations and obtain some parameters from empirical data. They were very important in computational chemistry from the 60s to the 90s, especially for treating large molecules where the full Hartree–Fock method without the approximations were too costly. The use of empirical parameters appears to allow some inclusion of correlation effects into the methods.

Primitive semi-empirical methods were designed even before, where the two-electron part of the Hamiltonian is not explicitly included. For π-electron systems, this was the Hückel method proposed by Erich Hückel, and for all valence electron systems, the extended Hückel method proposed by Roald Hoffmann. Sometimes, Hückel methods are referred to as "completely emprirical" because they do not derive from a Hamiltonian.[17] Yet, the term "empirical methods", or "empirical force fields" is usually used to describe Molecular Mechanics.[18]

Molecular mechanics

In many cases, large molecular systems can be modeled successfully while avoiding quantum mechanical calculations entirely. Molecular mechanics simulations, for example, use one classical expression for the energy of a compound, for instance, the harmonic oscillator. All constants appearing in the equations must be obtained beforehand from experimental data or *ab initio* calculations.

The database of compounds used for parameterization, i.e., the resulting set of parameters and functions is called the force field, is crucial to the success of molecular mechanics calculations. A force field parameterized against a specific class of molecules, for instance, proteins, would be expected to only have any relevance when describing other molecules of the same class.

These methods can be applied to proteins and other large biological molecules, and allow studies of the approach and interaction (docking) of potential drug molecules.[19][20]

Methods for solids

Computational chemical methods can be applied to solid-state physics problems. The electronic structure of a crystal is in general described by a band structure, which defines the energies of electron orbitals for each point in the Brillouin zone. Ab initio and semi-empirical calculations yield orbital energies; therefore, they can be applied to band structure calculations. Since it is time-consuming to calculate the energy for a molecule, it is even more time-consuming to calculate them for the entire list of points in the Brillouin zone.

Chemical dynamics

Once the electronic and nuclear variables are separated (within the Born–Oppenheimer representation), in the time-dependent approach, the wave packet corresponding to the nuclear degrees of freedom is propagated via the time evolution operator (physics) associated to the time-dependent Schrödinger equation (for the full molecular Hamiltonian). In the complementary energy-dependent approach, the time-independent Schrödinger equation is solved using the scattering theory formalism. The potential representing the interatomic interaction is given by the potential energy surfaces. In general, the potential energy surfaces are coupled via the vibronic coupling terms.

The most popular methods for propagating the wave packet associated to the molecular geometry are:

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- the split operator technique,
- the Chebyshev (real) polynomial,
- the multi-configuration time-dependent Hartree method (MCTDH),
- the semiclassical method.

Molecular dynamics

Molecular dynamics (MD) use either quantum mechanics, molecular mechanics or a mixture of both to calculate forces which are then used to solve Newton's laws of motion to examine the time-dependent behavior of systems. The result of a molecular dynamics simulation is a trajectory that describes how the position and velocity of particles varies with time. The phase point of a system described by the positions and momenta of all its particles on a previous time point will determine the next phase point in time by integrating over Newton's laws of motion.

Monte Carlo

Monte Carlo (MC) generates configurations of a system by making random changes to the positions of its particles, together with their orientations and conformations where appropriate. It is a random sampling method, which makes use of the so-called *importance sampling*. Importance sampling methods are able to generate low energy states, as this enables properties to be calculated accurately. The potential energy of each configuration of the system can be calculated, together with the values of other properties, from the positions of the atoms.[21][22]

Quantum mechanics/Molecular mechanics (QM/MM)

QM/MM is a hybrid method that attempts to combine the accuracy of quantum mechanics with the speed of molecular mechanics. It is useful for simulating very large molecules such as enzymes.

Interpreting molecular wave functions

The atoms in molecules (QTAIM) model of Richard Bader was developed to effectively link the quantum mechanical model of a molecule, as an electronic wavefunction, to chemically useful concepts such as atoms in molecules, functional groups, bonding, the theory of Lewis pairs, and the valence bond model. Bader has demonstrated that these empirically useful chemistry concepts can be related to the topology of the observable charge density distribution, whether measured or calculated from a quantum mechanical wavefunction. QTAIM analysis of molecular wavefunctions is implemented, for example, in the AIMAll software package.

Software packages

Many self-sufficient computational chemistry software packages exist. Some include many methods covering a wide range, while others concentrate on a very specific range or even on one method. Details of most of them can be found in:

- Biomolecular modelling programs: proteins, nucleic acid.
- Molecular mechanics programs.
- Quantum chemistry and solid state-physics software supporting several methods.
- Molecular design software
- Semi-empirical programs.
- Valence bond programs.

III. RESULTS

Drug studies may refer to:

- Clinical trials, experiments done to test the safety and effectiveness of medications
- The academic study of psychoactive drugs, chemical substances that alter perception, mood, consciousness or behavior

Clinical trials are prospective biomedical or behavioral research studies on human participants designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on dosage, safety and efficacy.[1][2] They are conducted only

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after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial—their approval does not mean the therapy is 'safe' or effective, only that the trial may be conducted.

Depending on product type and development stage, investigators initially enroll volunteers or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results.

Costs for clinical trials can range into the billions of dollars per approved drug.[3] and they take 11–14 years to complete.[4] The sponsor may be a governmental organization or a pharmaceutical, biotechnology or medical-device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory. Only 10 percent of all drugs started in human clinical trials become approved drugs.[5]

Trials of drugs

Some clinical trials involve healthy subjects with no pre-existing medical conditions. Other clinical trials pertain to people with specific health conditions who are willing to try an experimental treatment. Pilot experiments are conducted to gain insights for design of the clinical trial to follow.

There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy", or "effectiveness"; and to learn whether they are safe enough, called "safety".[1] Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks.[6][7]:8 For example, many drugs to treat cancer have severe side effects that would not be acceptable for an over-the-counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care and are used for a life-threatening condition.[8]

In the US the elderly constitute 14% of the population, while they consume over one-third of drugs.[9] People over 55 (or a similar cutoff age) are often excluded from trials because their greater health issues and drug use complicate data interpretation, and because they have different physiological capacity than younger people. Children and people with unrelated medical conditions are also frequently excluded.[10] Pregnant women are often excluded due to potential risks to the fetus.

The sponsor designs the trial in coordination with a panel of expert clinical investigators, including what alternative or existing treatments to compare to the new drug and what type(s) of patients might benefit. If the sponsor cannot obtain enough test subjects at one location investigators at other locations are recruited to join the study.

During the trial, investigators recruit subjects with the predetermined characteristics, administer the treatment(s) and collect data on the subjects' health for a defined time period. Data include measurements such as vital signs, concentration of the study drug in the blood or tissues, changes to symptoms, and whether improvement or worsening of the condition targeted by the study drug occurs. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.

Examples of clinical trial goals include assessing the safety and relative effectiveness of a medication or device:

- On a specific kind of patient
- At varying dosages
- For a new indication
- Evaluation for improved efficacy in treating a condition as compared to the standard therapy for that condition
- Evaluation of the study drug or device relative to two or more already approved/common interventions for that condition

While most clinical trials test one alternative to the novel intervention, some expand to three or four and may include a placebo.

Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol. The protocol is the trial's "operating manual" and ensures all researchers perform the trial in the same way on similar subjects and that the data is comparable across all subjects.

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As a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step.

The most common clinical trials evaluate new pharmaceutical products, medical devices, biologics, diagnostic assays, psychological therapies, or other interventions.[11] Clinical trials may be required before a national regulatory authority[12] approves marketing of the innovation.

Trials of devices

Similarly to drugs, manufacturers of medical devices in the United States are required to conduct clinical trials for premarket approval.[13] Device trials may compare a new device to an established therapy, or may compare similar devices to each other. An example of the former in the field of vascular surgery is the Open versus Endovascular Repair (OVER trial) for the treatment of abdominal aortic aneurysm, which compared the older open aortic repair technique to the newer endovascular aneurysm repair device.[14] An example of the latter are clinical trials on mechanical devices used in the management of adult female urinary incontinence.[15]

Trials of procedures

Similarly to drugs, medical or surgical procedures may be subjected to clinical trials,[16] such as comparing different surgical approaches in treatment of fibroids for subfertility.[17] However, when clinical trials are unethical or logistically impossible in the surgical setting, case-controlled studies will be replaced.[18]

Development

Although early medical experimentation was performed often, the use of a control group to provide an accurate comparison for the demonstration of the intervention's efficacy was generally lacking. For instance, Lady Mary Wortley Montagu, who campaigned for the introduction of inoculation (then called variolation) to prevent smallpox, arranged for seven prisoners who had been sentenced to death to undergo variolation in exchange for their life. Although they survived and did not contract smallpox, there was no control group to assess whether this result was due to the inoculation or some other factor. Similar experiments performed by Edward Jenner over his smallpox vaccine were equally conceptually flawed.[19]

The first proper clinical trial was conducted by the Scottish physician James Lind.[20] The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long-distance ocean voyages. In 1740, the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy.[21] John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but their use did not become widespread.[22]

Lind conducted the first systematic clinical trial in 1747.[23] He included a dietary supplement of an acidic quality in the experiment after two months at sea, when the ship was already afflicted with scurvy. He divided twelve scorbutic sailors into six groups of two. They all received the same diet but, in addition, group one was given a quart of cider daily, group two twenty-five drops of elixir of vitriol (sulfuric acid), group three six spoonfuls of vinegar, group four half a pint of seawater, group five received two oranges and one lemon, and the last group a spicy paste plus a drink of barley water. The treatment of group five stopped after six days when they ran out of fruit, but by then one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment.[24] Each year, May 20 is celebrated as Clinical Trials Day in honor of Lind's research.[25]

After 1750 the discipline began to take its modern shape.[26][27] The English doctor John Haygarth demonstrated the importance of a control group for the correct identification of the placebo effect in his celebrated study of the ineffective remedy called *Perkin's tractors*. Further work in that direction was carried out by the eminent physician Sir William Gull, 1st Baronet in the 1860s.[19]

Frederick Akbar Mahomed (d. 1884), who worked at Guy's Hospital in London, made substantial contributions to the process of clinical trials, where "he separated chronic nephritis with secondary hypertension from what we now term essential hypertension. He also founded the Collective Investigation Record for the British Medical Association; this organization collected data from physicians practicing outside the hospital setting and was the precursor of modern collaborative clinical trials."[28]

Modern trials

Sir Ronald A. Fisher, while working for the Rothamsted experimental station in the field of agriculture, developed his *Principles of experimental design* in the 1920s as an accurate methodology for the proper design of experiments.

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Among his major ideas, was the importance of randomization—the random assignment of individuals to different groups for the experiment;[29] replication—to reduce uncertainty, measurements should be repeated and experiments replicated to identify sources of variation;[30] blocking—to arrange experimental units into groups of units that are similar to each other, and thus reducing irrelevant sources of variation; use of factorial experiments—efficient at evaluating the effects and possible interactions of several independent factors.[19]

The British Medical Research Council officially recognized the importance of clinical trials from the 1930s. The council established the *Therapeutic Trials Committee* to advise and assist in the arrangement of properly controlled clinical trials on new products that seem likely on experimental grounds to have value in the treatment of disease.[19]

The first randomised curative trial was carried out at the MRC Tuberculosis Research Unit by Sir Geoffrey Marshall (1887–1982). The trial, carried out between 1946 and 1947, aimed to test the efficacy of the chemical streptomycin for curing pulmonary tuberculosis. The trial was both double-blind and placebo-controlled.[31]

The methodology of clinical trials was further developed by Sir Austin Bradford Hill, who had been involved in the streptomycin trials. From the 1920s, Hill applied statistics to medicine, attending the lectures of renowned mathematician Karl Pearson, among others. He became famous for a landmark study carried out in collaboration with Richard Doll on the correlation between smoking and lung cancer. They carried out a case-control study in 1950, which compared lung cancer patients with matched control and also began a sustained long-term prospective study into the broader issue of smoking and health, which involved studying the smoking habits and health of more than 30,000 doctors over a period of several years. His certificate for election to the Royal Society called him "... the leader in the development in medicine of the precise experimental methods now used nationally and internationally in the evaluation of new therapeutic and prophylactic agents."

International clinical trials day is celebrated on 20 May.[32]

The acronyms used in the titling of clinical trials is often contrived, and has been the subject of derision.[33]

Types

Clinical trials are classified by the research objective created by the investigators.[11]

- In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.[34]
- In an *interventional study*, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes.[34]

Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type:[11]

- *Prevention* trials look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.
- *Screening* trials test for ways to identify certain diseases or health conditions.
- *Diagnostic* trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- *Treatment* trials test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.
- *Quality of life* trials (supportive care trials) evaluate how to improve comfort and quality of care for people with a chronic illness.
- *Genetic* trials are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.
- *Epidemiological* trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.
- *Compassionate use* trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too

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compromised to qualify for participation in randomized clinical trials.[35] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

- Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.
- Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.[36] Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.[37] The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.[38][39]

Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.[11]

Phases

National Cancer Institute video on the phases of clinical trials

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug development process will normally proceed through phases I–IV over many years, frequently involving a decade or longer. If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.[11] Phase IV trials are performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.[11]

Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[40] For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase I	Screening for safety	Often are first-in-person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.[11]
Phase II	Establishing the preliminary efficacy of the drug in a "treatment group", usually against a placebo control group	Phase II-a is specifically designed to assess dosing requirements (how much drug should be given),[11][41] while a Phase IIb trial is designed to determine efficacy, and studies how well the drug works at the prescribed dose(s), establishing a therapeutic dose range.[41]

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Phase III	Final confirmation of safety and efficacy	Testing with large groups of people (typically 1,000–3,000) to confirm drug efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.[11]
Phase IV	Safety studies during sales	Postmarketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.[11]

Trial design

A fundamental distinction in evidence-based practice is between observational studies and randomized controlled trials.[42] Types of observational studies in epidemiology, such as the cohort study and the case-control study, provide less compelling evidence than the randomized controlled trial.[42] In observational studies, the investigators retrospectively assess associations between the treatments given to participants and their health status, with potential for considerable errors in design and interpretation.[43]

A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.[42]

Some Phase II and most Phase III drug trials are designed as randomized, double-blind, and placebo-controlled.

- Randomized: Each study subject is randomly assigned to receive either the study treatment or a placebo.
- Blind: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives. This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.
- Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Clinical studies having small numbers of subjects may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions or feasibility to expand the research for a more comprehensive randomized controlled trial.[44]

Clinical studies can be "sponsored" (financed and organized) by academic institutions, pharmaceutical companies, government entities and even private groups. Trials are conducted for new drugs, biotechnology, diagnostic assays or medical devices to determine their safety and efficacy prior to being submitted for regulatory review that would determine market approval.

Active control studies

In many cases, giving a placebo to a person suffering from a disease may be unethical.[45] To address this, it has become a common practice to conduct "active comparator" (also known as "active control") trials. In trials with an active control group, subjects are given either the experimental treatment or a previously approved treatment with known effectiveness.

Master protocol

In such studies multiple experimental treatments are tested in a single trial. Genetic testing enables researchers to group patients according to their genetic profile, deliver drugs based on that profile to that group and compare the results. Multiple companies can participate, each bringing a different drug. The first such approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer are

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involved, the first time they have worked together in a late-stage trial. Patients whose genomic profiles do not match any of the trial drugs receive a drug designed to stimulate the immune system to attack cancer.[46]

Clinical trial protocol

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts. All study investigators are expected to strictly observe the protocol.

The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure.

The protocol contains a precise study plan to assure safety and health of the trial subjects and to provide an exact template for trial conduct by investigators. This allows data to be combined across all investigators/sites. The protocol also informs the study administrators (often a contract research organization).

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan have been standardized to follow Good Clinical Practice guidance[47] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[48] Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as *Trials*, encourage investigators to publish their protocols.

Design features

Informed consent

Clinical trials recruit study subjects to sign a document representing their "informed consent".[49] The document includes details such as its purpose, duration, required procedures, risks, potential benefits, key contacts and institutional requirements.[50] The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty.

Informed consent is a legal process in which a recruit is instructed about key facts before deciding whether to participate.[49] Researchers explain the details of the study in terms the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent.

Statistical power

In any clinical trial, the number of subjects, also called the sample size, has a large impact on the ability to reliably detect and measure the effects of the intervention. This ability is described as its "power", which must be calculated before initiating a study to figure out if the study is worth its costs.[51] In general, a larger sample size increases the statistical power, also the cost.

The statistical power estimates the ability of a trial to detect a difference of a particular size (or larger) between the treatment and control groups. For example, a trial of a lipid-lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 6 mg/dL.

Placebo groups

Merely giving a treatment can have nonspecific effects. These are controlled for by the inclusion of patients who receive only a placebo. Subjects are assigned randomly without informing them to which group they belonged. Many trials are doubled-blinded so that researchers do not know to which group a subject is assigned.

Assigning a subject to a placebo group can pose an ethical problem if it violates his or her right to receive the best available treatment. The Declaration of Helsinki provides guidelines on this issue.

Duration

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.[52] For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials. But the major holdup in making new cancer drugs available is the time it takes to complete

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clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public.[53] Drugs for other diseases have similar timelines.

Some reasons a clinical trial might last several years:

- For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.
- For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.
- Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat these particular patients must participate in the trial. Then they must identify the desirable patients and obtain consent from them or their families to take part in the trial.

A clinical trial might also include an extended post-study follow-up period from months to years for people who have participated in the trial, a so-called "extension phase", which aims to identify long-term impact of the treatment.[54]

The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were being tested in clinical trials in 2005. Not all of these will prove to be useful, but those that are may be delayed in getting approved because the number of participants is so low .[55]

For clinical trials involving potential for seasonal influences (such as airborne allergies, seasonal affective disorder, influenza, and skin diseases), the study may be done during a limited part of the year (such as spring for pollen allergies), when the drug can be tested.[56][57]

Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies, such as the Nurses' Health Study).

Administration

Clinical trials designed by a local investigator, and (in the US) federally funded clinical trials, are almost always administered by the researcher who designed the study and applied for the grant. Small-scale device studies may be administered by the sponsoring company. Clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company. The sponsor provides the drug and medical oversight. A CRO is contracted to perform all the administrative work on a clinical trial. For Phases II–IV the CRO recruits participating researchers, trains them, provides them with supplies, coordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures the sponsor receives data from every site. Specialist site management organizations can also be hired to coordinate with the CRO to ensure rapid IRB/IEC approval and faster site initiation and patient recruitment. Phase I clinical trials of new medicines are often conducted in a specialist clinical trial clinic, with dedicated pharmacologists, where the subjects can be observed by full-time staff. These clinics are often run by a CRO which specialises in these studies.

At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial. The research assistant's job can include some or all of the following: providing the local institutional review board (IRB) with the documentation necessary to obtain its permission to conduct the study, assisting with study start-up, identifying eligible patients, obtaining consent from them or their families, administering study treatment(s), collecting and statistically analyzing data, maintaining and updating data files during followup, and communicating with the IRB, as well as the sponsor and CRO.

Quality

In the context of a clinical trial, quality typically refers to the absence of errors which can impact decision making, both during the conduct of the trial and in use of the trial results.[58]

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Marketing

An Interactional Justice Model may be used to test the effects of willingness to talk with a doctor about clinical trial enrollment.[59] Results found that potential clinical trial candidates were less likely to enroll in clinical trials if the patient is more willing to talk with their doctor. The reasoning behind this discovery may be patients are happy with their current care. Another reason for the negative relationship between perceived fairness and clinical trial enrollment is the lack of independence from the care provider. Results found that there is a positive relationship between a lack of willingness to talk with their doctor and clinical trial enrollment. Lack of willingness to talk about clinical trials with current care providers may be due to patients' independence from the doctor. Patients who are less likely to talk about clinical trials are more willing to use other sources of information to gain a better insight of alternative treatments. Clinical trial enrollment should be motivated to utilize websites and television advertising to inform the public about clinical trial enrollment.

Information technology

The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials. Clinical trial management systems are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites. Advanced analytics for identifying researchers and research sites with expertise in a given area utilize public and private information about ongoing research.[60] Web-based electronic data capture (EDC) and clinical data management systems are used in a majority of clinical trials[61] to collect case report data from sites, manage its quality and prepare it for analysis. Interactive voice response systems are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm (although phones are being increasingly replaced with web-based (IWRS) tools which are sometimes part of the EDC system). While patient-reported outcome were often paper based in the past, measurements are increasingly being collected using web portals or hand-held ePRO (or eDiary) devices, sometimes wireless.[62] Statistical software is used to analyze the collected data and prepare them for regulatory submission. Access to many of these applications are increasingly aggregated in web-based clinical trial portals. In 2011, the FDA approved a Phase I trial that used telemonitoring, also known as remote patient monitoring, to collect biometric data in patients' homes and transmit it electronically to the trial database. This technology provides many more data points and is far more convenient for patients, because they have fewer visits to trial sites.

Analysis

A clinical trial produces data that could reveal quantitative differences between two or more interventions; statistical analyses are used to determine whether such differences are true, result from chance, or are the same as no treatment (placebo).[63][64] Data from a clinical trial accumulate gradually over the trial duration, extending from months to years.[49] Accordingly, results for participants recruited early in the study become available for analysis while subjects are still being assigned to treatment groups in the trial. Early analysis may allow the emerging evidence to assist decisions about whether to stop the study, or to reassign participants to the more successful segment of the trial.[63] Investigators may also want to stop a trial when data analysis shows no treatment effect.[64]

Ethical aspects

Clinical trials are closely supervised by appropriate regulatory authorities. All studies involving a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise noninterventional studies (observational studies or those using already collected data). In the US, this body is called the Institutional Review Board (IRB); in the EU, they are called Ethics committees. Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.

To be ethical, researchers must obtain the full and informed consent of participating human subjects. (One of the IRB's main functions is to ensure potential patients are adequately informed about the clinical trial.) If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. In addition, the clinical trial participants must be made aware that they can withdraw from the clinical trial at any time without any adverse action taken against them.[65] In California, the state has prioritized the individuals who can serve as the legally authorized representative.[66]

In some US locations, the local IRB must certify researchers and their staff before they can conduct clinical trials. They must understand the federal patient privacy (HIPAA) law and good clinical practice. The International Conference of

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Harmonisation Guidelines for Good Clinical Practice is a set of standards used internationally for the conduct of clinical trials. The guidelines aim to ensure the "rights, safety and well being of trial subjects are protected".

The notion of informed consent of participating human subjects exists in many countries but its precise definition may still vary.

Informed consent is clearly a 'necessary' condition for ethical conduct but does not 'ensure' ethical conduct. In compassionate use trials the latter becomes a particularly difficult problem. The final objective is to serve the community of patients or future patients in a best-possible and most responsible way. See also Expanded access. However, it may be hard to turn this objective into a well-defined, quantified, objective function. In some cases this can be done, however, for instance, for questions of when to stop sequential treatments (see Odds algorithm), and then quantified methods may play an important role.

Additional ethical concerns are present when conducting clinical trials on children (pediatrics), and in emergency or epidemic situations.[67][68]

Ethically balancing the rights of multiple stakeholders may be difficult. For example, when drug trials fail, the sponsors may have a duty to tell current and potential investors immediately, which means both the research staff and the enrolled participants may first hear about the end of a trial through public business news.[69]

Conflicts of interest and unfavorable studies

In response to specific cases in which unfavorable data from pharmaceutical company-sponsored research were not published, the Pharmaceutical Research and Manufacturers of America published new guidelines urging companies to report all findings and limit the financial involvement in drug companies by researchers.[70] The US Congress signed into law a bill which requires Phase II and Phase III clinical trials to be registered by the sponsor on the clinicaltrials.gov website compiled by the National Institutes of Health.[71]

Drug researchers not directly employed by pharmaceutical companies often seek grants from manufacturers, and manufacturers often look to academic researchers to conduct studies within networks of universities and their hospitals, e.g., for translational cancer research. Similarly, competition for tenured academic positions, government grants and prestige create conflicts of interest among academic scientists.[72] According to one study, approximately 75% of articles retracted for misconduct-related reasons have no declared industry financial support.[73] Seeding trials are particularly controversial.[74]

In the United States, all clinical trials submitted to the FDA as part of a drug approval process are independently assessed by clinical experts within the Food and Drug Administration,[75] including inspections of primary data collection at selected clinical trial sites.[76]

In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000, received 60% of the grants from pharmaceutical companies in the US. Researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.[77]

Despite explicit recommendations by stakeholders of measures to improve the standards of industry-sponsored medical research,[78] in 2013, Tohen warned of the persistence of a gap in the credibility of conclusions arising from industry-funded clinical trials, and called for ensuring strict adherence to ethical standards in industrial collaborations with academia, in order to avoid further erosion of the public's trust.[79] Issues referred for attention in this respect include potential observation bias, duration of the observation time for maintenance studies, the selection of the patient populations, factors that affect placebo response, and funding sources.[80][81][82]

During public health crisis

Conducting clinical trials of vaccines during epidemics and pandemics is subject to ethical concerns. For diseases with high mortality rates like Ebola, assigning individuals to a placebo or control group can be viewed as a death sentence. In response to ethical concerns regarding clinical research during epidemics, the National Academy of Medicine authored a report identifying seven ethical and scientific considerations. These considerations are:[83]

- Scientific value
- Social value

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- Respect for persons
- Community engagement
- Concern for participant welfare and interests
- A balance towards benefit over risks
- Post-trial access to tested therapies that had been withheld during the trial

Pregnant women and children

Pregnant women and children are typically excluded from clinical trials as vulnerable populations, though the data to support excluding them is not robust. By excluding them from clinical trials, information about the safety and effectiveness of therapies for these populations is often lacking. During the early history of the HIV/AIDS epidemic, a scientist noted that by excluding these groups from potentially life-saving treatment, they were being "protected to death". Projects such as Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) have advocated for the ethical inclusion of pregnant women in vaccine trials. Inclusion of children in clinical trials has additional moral considerations, as children lack decision-making autonomy. Trials in the past had been criticized for using hospitalized children or orphans; these ethical concerns effectively stopped future research. In efforts to maintain effective pediatric care, several European countries and the US have policies to entice or compel pharmaceutical companies to conduct pediatric trials. International guidance recommends ethical pediatric trials by limiting harm, considering varied risks, and taking into account the complexities of pediatric care.[83]

Safety

Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device), the regulatory agency for the country where the drug or device will be sold.

A systematic concurrent safety review is frequently employed to assure research participant safety. The conduct and on-going review is designed to be proportional to the risk of the trial. Typically this role is filled by a Data and Safety Committee, an externally appointed Medical Safety Monitor,[84] an Independent Safety Officer, or for small or low-risk studies the principal investigator.[85]

For safety reasons, many clinical trials of drugs[86] are designed to exclude women of childbearing age, pregnant women, or women who become pregnant during the study. In some cases, the male partners of these women are also excluded or required to take birth control measures.

Sponsor

Throughout the clinical trial, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved treatments. This allows the local investigators to make an informed judgment on whether to participate in the study or not. The sponsor is also responsible for monitoring the results of the study as they come in from the various sites as the trial proceeds. In larger clinical trials, a sponsor will use the services of a data monitoring committee (DMC, known in the US as a data safety monitoring board). This independent group of clinicians and statisticians meets periodically to review the unblinded data the sponsor has received so far. The DMC has the power to recommend termination of the study based on their review, for example if the study treatment is causing more deaths than the standard treatment, or seems to be causing unexpected and study-related serious adverse events. The sponsor is responsible for collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment.

The sponsor and the local site investigators are jointly responsible for writing a site-specific informed consent that accurately informs the potential subjects of the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language. FDA regulations state that participating in clinical trials is voluntary, with the subject having the right not to participate or to end participation at any time.[87]

Local site investigators

The ethical principle of *primum non-nocere* ("first, do no harm") guides the trial, and if an investigator believes the study treatment may be harming subjects in the study, the investigator can stop participating at any time. On the other

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hand, investigators often have a financial interest in recruiting subjects, and could act unethically to obtain and maintain their participation.

The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study. The local investigator or his/her study staff are also responsible for ensuring the potential subjects in the study understand the risks and potential benefits of participating in the study. In other words, they (or their legally authorized representatives) must give truly informed consent.

Local investigators are responsible for reviewing all adverse event reports sent by the sponsor. These adverse event reports contain the opinions of both the investigator (at the site where the adverse event occurred) and the sponsor, regarding the relationship of the adverse event to the study treatments. Local investigators also are responsible for making an independent judgment of these reports, and promptly informing the local IRB of all serious and study treatment-related adverse events.

When a local investigator is the sponsor, there may not be formal adverse event reports, but study staff at all locations are responsible for informing the coordinating investigator of anything unexpected. The local investigator is responsible for being truthful to the local IRB in all communications relating to the study.

Institutional review boards (IRBs)

Approval by an Institutional Review Board (IRB), or Independent Ethics Committee (IEC), is necessary before all but the most informal research can begin. In commercial clinical trials, the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial. However, the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol, the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs. Other researchers (such as in walk-in clinics) use independent IRBs.

The IRB scrutinizes the study both for medical safety and for protection of the patients involved in the study, before it allows the researcher to begin the study. It may require changes in study procedures or in the explanations given to the patient. A required yearly "continuing review" report from the investigator updates the IRB on the progress of the study and any new safety information related to the study.

Regulatory agencies

In the US, the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data). Avoiding an audit is an incentive for investigators to follow study procedures. A 'covered clinical study' refers to a trial submitted to the FDA as part of a marketing application (for example, as part of an NDA or 510(k)), about which the FDA may require disclosure of financial interest of the clinical investigator in the outcome of the study. For example, the applicant must disclose whether an investigator owns equity in the sponsor, or owns proprietary interest in the product under investigation. The FDA defines a covered study as "... any study of a drug, biological product or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety."[88]

Alternatively, many American pharmaceutical companies have moved some clinical trials overseas. Benefits of conducting trials abroad include lower costs (in some countries) and the ability to run larger trials in shorter timeframes, whereas a potential disadvantage exists in lower-quality trial management.[89] Different countries have different regulatory requirements and enforcement abilities. An estimated 40% of all clinical trials now take place in Asia, Eastern Europe, and Central and South America. "There is no compulsory registration system for clinical trials in these countries and many do not follow European directives in their operations", says Jacob Sijtsma of the Netherlands-based WEMOS, an advocacy health organisation tracking clinical trials in developing countries.[90]

Beginning in the 1980s, harmonization of clinical trial protocols was shown as feasible across countries of the European Union. At the same time, coordination between Europe, Japan and the United States led to a joint regulatory-industry initiative on international harmonization named after 1990 as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[91] Currently, most clinical trial programs follow ICH guidelines, aimed at "ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer

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and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness."[92]

Aggregation of safety data during clinical development

Aggregating safety data across clinical trials during drug development is important because trials are generally designed to focus on determining how well the drug works. The safety data collected and aggregated across multiple trials as the drug is developed allows the sponsor, investigators and regulatory agencies to monitor the aggregate safety profile of experimental medicines as they are developed. The value of assessing aggregate safety data is: a) decisions based on aggregate safety assessment during development of the medicine can be made throughout the medicine's development and b) it sets up the sponsor and regulators well for assessing the medicine's safety after the drug is approved.[93][94][95][96][97]

Economics

Clinical trial costs vary depending on trial phase, type of trial, and disease studied. A study of clinical trials conducted in the United States from 2004 to 2012 found the average cost of Phase I trials to be between $1.4 million and $6.6 million, depending on the type of disease. Phase II trials ranged from $7 million to $20 million, and Phase III trials from $11 million to $53 million.[98]

Sponsor

The cost of a study depends on many factors, especially the number of sites conducting the study, the number of patients involved, and whether the study treatment is already approved for medical use.

The expenses incurred by a pharmaceutical company in administering a Phase III or IV clinical trial may include, among others:

- production of the drug(s) or device(s) being evaluated
- staff salaries for the designers and administrators of the trial
- payments to the contract research organization, the site management organization (if used) and any outside consultants
- payments to local researchers and their staff for their time and effort in recruiting test subjects and collecting data for the sponsor
- the cost of study materials and the charges incurred to ship them
- communication with the local researchers, including on-site monitoring by the CRO before and (in some cases) multiple times during the study
- one or more investigator training meetings
- expense incurred by the local researchers, such as pharmacy fees, IRB fees and postage
- any payments to subjects enrolled in the trial
- the expense of treating a test subject who develops a medical condition caused by the study drug

These expenses are incurred over several years.

In the US, sponsors may receive a 50 percent tax credit for clinical trials conducted on drugs being developed for the treatment of orphan diseases.[99] National health agencies, such as the US National Institutes of Health, offer grants to investigators who design clinical trials that attempt to answer research questions of interest to the agency. In these cases, the investigator who writes the grant and administers the study acts as the sponsor, and coordinates data collection from any other sites. These other sites may or may not be paid for participating in the study, depending on the amount of the grant and the amount of effort expected from them. Using internet resources can, in some cases, reduce the economic burden.[100]

Investigators

Investigators are often compensated for their work in clinical trials. These amounts can be small, just covering a partial salary for research assistants and the cost of any supplies (usually the case with national health agency studies), or be substantial and include "overhead" that allows the investigator to pay the research staff during times between clinical trials.[*citation needed*]

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Subjects

Participants in Phase I drug trials do not gain any direct health benefit from taking part. They are generally paid a fee for their time, with payments regulated and not related to any risk involved. Motivations of healthy volunteers is not limited to financial reward and may include other motivations such as contributing to science and others.[101] In later phase trials, subjects may not be paid to ensure their motivation for participating with potential for a health benefit or contributing to medical knowledge. Small payments may be made for study-related expenses such as travel or as compensation for their time in providing follow-up information about their health after the trial treatment ends.

Participant recruitment and participation

Phase 0 and Phase I drug trials seek healthy volunteers. Most other clinical trials seek patients who have a specific disease or medical condition. The diversity observed in society should be reflected in clinical trials through the appropriate inclusion of ethnic minority populations.[102] Patient recruitment or participant recruitment plays a significant role in the activities and responsibilities of sites conducting clinical trials.[103]

All volunteers being considered for a trial are required to undertake a medical screening. Requirements differ according to the trial needs, but typically volunteers would be screened in a medical laboratory for:[104]

- Measurement of the electrical activity of the heart (ECG)
- Measurement of blood pressure, heart rate, and body temperature
- Blood sampling
- Urine sampling
- Weight and height measurement
- Drug abuse testing
- Pregnancy testing

It has been observed that participants in clinical trials are disproportionately white.[105][106] Often, minorities are not informed about clinical trials.[107] One recent systematic review of the literature found that race/ethnicity as well as sex were not well-represented nor at times even tracked as participants in a large number of clinical trials of hearing loss management in adults.[108] This may reduce the validity of findings in respect of non-white patients[109] by not adequately representing the larger populations.

Locating trials

Depending on the kind of participants required, sponsors of clinical trials, or contract research organizations working on their behalf, try to find sites with qualified personnel as well as access to patients who could participate in the trial. Working with those sites, they may use various recruitment strategies, including patient databases, newspaper and radio advertisements, flyers, posters in places the patients might go (such as doctor's offices), and personal recruitment of patients by investigators.

Volunteers with specific conditions or diseases have additional online resources to help them locate clinical trials. For example, the Fox Trial Finder connects Parkinson's disease trials around the world to volunteers who have a specific set of criteria such as location, age, and symptoms.[110] Other disease-specific services exist for volunteers to find trials related to their condition.[111] Volunteers may search directly on ClinicalTrials.gov to locate trials using a registry run by the U.S. National Institutes of Health and National Library of Medicine. There also is software that allows clinicians to find trial options for an individual patient based on data such as genomic data.[112]

The risk information seeking and processing (RISP) model analyzes social implications that affect attitudes and decision making pertaining to clinical trials.[113] People who hold a higher stake or interest in the treatment provided in a clinical trial showed a greater likelihood of seeking information about clinical trials. Cancer patients reported more optimistic attitudes towards clinical trials than the general population. Having a more optimistic outlook on clinical trials also leads to greater likelihood of enrolling.[113]

Decentralized trials

Although trials are commonly conducted at major medical centers, some participants are excluded due to the distance and expenses required for travel, leading to hardship, disadvantage, and inequity for participants, especially those in rural and underserved communities. In the 21st century, efforts are made to collect information within a participant's home, a capability improved by telehealth and wearable technologies.[114]

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IV. CONCLUSION

A **psychoactive drug**, **psychopharmaceutical**, **psychoactive agent**, or **psychotropic drug** is a chemical substance that changes the function of the nervous system and results in alterations of perception, mood, cognition, and behavior.[1] These substances may be used medically, recreationally, for spiritual reasons (for example, by altering one's consciousness, as with entheogens for ritual, spiritual, or shamanic purposes), or for research. Some categories of psychoactive drugs may be prescribed by physicians[2] and other healthcare practitioners because of their therapeutic value.

Some psychoactive substances may be used in detoxification and rehabilitation programs for people who may have become dependent upon or addicted to other mind-altering or mood-altering substances. Drug rehabilitation attempts to reduce addiction through a combination of psychotherapy, support groups, and sometimes psychoactive substances.

Psychoactive substances often bring various changes in consciousness and mood that the user may find rewarding and pleasant (e.g., euphoria or a sense of relaxation) or advantageous in an objectively observable or measurable way (e.g., increased alertness). Substances that are rewarding and thus positively reinforcing have the potential to induce a state of addiction – compulsive drug use despite negative consequences. In addition, sustained use of some substances may produce physical or psychological dependence, or both, associated with somatic or psychological-emotional withdrawal states, respectively.

Psychoactive drug misuse, dependence, and addiction have resulted in legal measures and moral debate. Governmental controls on manufacture, supply, and prescription attempt to reduce problematic medical drug use. Ethical concerns have also been raised about the overuse of these drugs clinically and about their marketing by manufacturers. Popular campaigns to decriminalize[3] or legalize the recreational use of certain drugs (e.g., cannabis) are also ongoing.

Alcohol is a widely-used psychoactive drug. The global alcoholic drinks market was expected to exceed $1 trillion in 2013.[4] Beer is the world's third-most popular drink, after water and tea.[5]

Psychoactive drug use can be traced back to prehistory. There is archaeological evidence of the use of psychoactive substances, mostly plants, dating back at least 10,000 years and historical evidence of cultural use over the past 5,000 years.[6] The chewing of coca leaves, for example, dates back over 8,000 years ago in Peruvian society.[7][8]

Medicinal use is one important facet of psychoactive drug use. However, some have postulated that the urge to alter one's consciousness is as primary as the drive to satiate thirst, hunger, or sexual desire.[9] Supporters of this belief contend that the history of drug use, and even children's desire for spinning, swinging, or sliding indicate that the drive to alter one's state of mind is universal.[10]

One of the first people to articulate this point of view, set aside from a medicinal context, was American author Fitz Hugh Ludlow (1836–1870) in his book *The Hasheesh Eater* (1857):

[D]rugs are able to bring humans into the neighborhood of divine experience and can thus carry us up from our personal fate and the everyday circumstances of our life into a higher form of reality. It is, however, necessary to understand precisely what is meant by the use of drugs. We do not mean the purely physical craving ... That of which we speak is something much higher, namely the knowledge of the possibility of the soul to enter into a lighter being, and to catch a glimpse of deeper insights and more magnificent visions of the beauty, truth, and the divine than we are normally able to spy through the cracks in our prison cell. But there are not many drugs which have the power of stilling such craving. The entire catalog, at least to the extent that research has thus far written it, may include only opium, hashish, and in rarer cases alcohol, which has enlightening effects only upon very particular characters.[11]

During the 20th century, many governments across the world initially responded to the use of recreational drugs by banning use, production, or distribution of them, and making their use, supply, or trade a criminal offense. A notable example of this was Prohibition in the United States, where alcohol was made illegal for 13 years. However, many governments, government officials, and persons in law enforcement have concluded that illicit drug use cannot be sufficiently stopped through criminalization. Organizations such as Law Enforcement Against Prohibition (LEAP) have come to such a conclusion, believing:

[T]he existing drug policies have failed in their intended goals of addressing the problems of crime, drug abuse, addiction, juvenile drug use, stopping the flow of illegal drugs into this country and the internal sale and use of illegal drugs. By fighting a war on drugs the government has increased the problems of society and made them far worse. A system of regulation rather than prohibition is a less harmful, more ethical and a more effective public policy.[12][

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In some countries, there has been a move toward harm reduction by health services, where the use of illicit drugs is neither condoned nor promoted, but services and support are provided to ensure users have adequate factual information readily available, and that the negative effects of their use be minimized. Such is the case of the Portuguese drug policy of decriminalization, which achieved its primary goal of reducing the adverse health effects of drug abuse.[13]

Purposes

Psychoactive substances are used for a number of different purposes, and these uses vary widely between cultures. Some substances may have controlled or illegal uses; typically used medicinally, but other uses do exist. Other examples include social drinking, nootropics, or sleep aids. Caffeine is the world's most widely consumed psychoactive substance, but unlike many others, it is legal and unregulated in nearly all jurisdictions. In North America, 90% of adults consume caffeine daily.[14]

Psychoactive drugs are divided into different groups according to their pharmacological effects. Commonly used psychoactive drugs and groups are listed below:

- Anxiolytics. Medicinally used to reduce the symptoms of anxiety, and sometimes insomnia.

Example: benzodiazepines such as Xanax and Valium; barbiturates

- Empathogen–entactogens. A drug class that alters one's emotional state, often resulting in an increased sense of empathy, closeness, and emotional communication.

Example: MDMA (ecstasy), MDA, 6-APB, AMT

- Stimulants (colloquially referred to as "uppers"). This category comprises substances that increase wakefulness and productivity, stimulate the nervous system, and may cause euphoria, but are not known to typically cause hallucinatory effects. Some stimulants are used medicinally to treat individuals with ADHD and Narcolepsy.

Examples: amphetamines, caffeine, cocaine, nicotine

- Depressants (colloquially referred to as "downers"), including sedatives, hypnotics, and opioids. This classification encompasses a spectrum of substances with sedative, soporific, and anesthetic properties.

Examples: Ethanol (alcohol), opioids such as morphine, fentanyl, and codeine, cannabis, barbiturates, and benzodiazepines.

- Hallucinogens, including psychedelics, dissociatives, and deliriants. This category encompasses all substances that produce distinct alterations in perception, sensation of space and time, and emotional states.[15]

Examples: psilocybin, LSD, DMT (N,N-Dimethyltryptamine)/ayahuasca, mescaline, Salvia divinorum, Nitrous oxide, and Scopolamine

Anesthesia

General anesthetics are a class of psychoactive drug used on people to block physical pain and other sensations. Most anesthetics induce unconsciousness, allowing the person to undergo medical procedures like surgery, without the feelings of physical pain or emotional trauma.[16] To induce unconsciousness, anesthetics affect the GABA and NMDA systems. For example, Propofol is a GABA agonist,[17] and ketamine is an NMDA receptor antagonist.[18]

Pain management

Psychoactive drugs are often prescribed to manage pain. The subjective experience of pain is primarily regulated by endogenous opioid peptides. Thus, pain can often be managed using psychoactives that operate on this neurotransmitter system, also known as opioid receptor agonists. This class of drugs can be highly addictive, and includes opiate narcotics, like morphine and codeine.[19] NSAIDs, such as aspirin and ibuprofen, are also analgesics. These agents also reduce eicosanoid-mediated inflammation by inhibiting the enzyme cyclooxygenase.

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Mental disorders

Psychiatric medications are psychoactive drugs prescribed for the management of mental and emotional disorders, or to aid in overcoming challenging behavior.[20] There are six major classes of psychiatric medications:

- Antidepressants treat disorders such as clinical depression, dysthymia, anxiety, eating disorders and borderline personality disorder.[21]
- Stimulants, used to treat disorders such as attention deficit hyperactivity disorder and narcolepsy, and for weight reduction.
- Antipsychotics, used to treat psychotic symptoms, such as those associated with schizophrenia or severe mania, or as adjuncts to relieve clinical depression.
- Mood stabilizers, used to treat bipolar disorder and schizoaffective disorder.
- Anxiolytics, used to treat anxiety disorders.
- Depressants, used as hypnotics, sedatives, and anesthetics, depending upon dosage.

In addition, several psychoactive substances are currently employed to treat various addictions. These include acamprosate or naltrexone in the treatment of alcoholism, or methadone or buprenorphine maintenance therapy in the case of opioid addiction.[22]

Exposure to psychoactive drugs can cause changes to the brain that counteract or augment some of their effects; these changes may be beneficial or harmful. However, there is a significant amount of evidence that the relapse rate of mental disorders negatively corresponds with the length of properly followed treatment regimens (that is, relapse rate substantially declines over time), and to a much greater degree than placebo.[23]

Recreation

Many psychoactive substances are used for their mood and perception altering effects, including those with accepted uses in medicine and psychiatry. Examples of psychoactive substances include caffeine, alcohol, cocaine, LSD, nicotine and cannabis.[24] Classes of drugs frequently used recreationally include:

- Stimulants, which activate the central nervous system. These are used recreationally for their euphoric effects.
- Hallucinogens (psychedelics, dissociatives and deliriants), which induce perceptual and cognitive alterations.
- Hypnotics, which depress the central nervous system.
- Opioid analgesics, which also depress the central nervous system. These are used recreationally because of their euphoric effects.
- Inhalants, in the forms of gas aerosols, or solvents, which are inhaled as a vapor because of their stupefying effects. Many inhalants also fall into the above categories (such as nitrous oxide which is also an analgesic).

In some modern and ancient cultures, drug usage is seen as a status symbol. Recreational drugs are seen as status symbols in settings such as at nightclubs and parties.[25] For example, in ancient Egypt, gods were commonly pictured holding hallucinogenic plants.[26]

Because there is controversy about regulation of recreational drugs, there is an ongoing debate about drug prohibition. Critics of prohibition believe that regulation of recreational drug use is a violation of personal autonomy and freedom.[27] In the United States, critics have noted that prohibition or regulation of recreational and spiritual drug use might be unconstitutional, and causing more harm than is prevented.[28]

Some people who take psychoactive drugs experience drug or substance induced psychosis. A 2019 systematic review and meta-analysis by Murrie et al. found that the pooled proportion of transition from substance-induced psychosis to schizophrenia was 25% (95% CI 18%–35%), compared with 36% (95% CI 30%–43%) for brief, atypical and not otherwise specified psychoses.[29] Type of substance was the primary predictor of transition from drug-induced psychosis to schizophrenia, with highest rates associated with cannabis (6 studies, 34%, CI 25%–46%), hallucinogens (3 studies, 26%, CI 14%–43%) and amphetamines (5 studies, 22%, CI 14%–34%). Lower rates were reported for opioid (12%), alcohol (10%) and sedative (9%) induced psychoses. Transition rates were slightly lower in older cohorts but were not affected by sex, country of the study, hospital or community location, urban or rural setting, diagnostic methods, or duration of follow-up.[29]

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Ritual and spiritual

Certain psychoactives, particularly hallucinogens, have been used for religious purposes since prehistoric times. Native Americans have used peyote cacti containing mescaline for religious ceremonies for as long as 5700 years.[30] The muscimol-containing *Amanita muscaria* mushroom was used for ritual purposes throughout prehistoric Europe.[31]

The use of entheogens for religious purposes resurfaced in the West during the counterculture movements of the 1960s and 70s. Under the leadership of Timothy Leary, new spiritual and intention-based movements began to use LSD and other hallucinogens as tools to access deeper inner exploration. In the United States, the use of peyote for ritual purposes is protected only for members of the Native American Church, which is allowed to cultivate and distribute peyote. However, the genuine religious use of peyote, regardless of one's personal ancestry, is protected in Colorado, Arizona, New Mexico, Nevada, and Oregon.[32]

Military

Psychoactive drugs have been used in military applications as non-lethal weapons.

Both military and civilian American intelligence officials are known to have used psychoactive drugs while interrogating captives apprehended in its *"war on terror"*. In July 2012 Jason Leopold and Jeffrey Kaye, psychologists and human rights workers, had a Freedom of Information Act request fulfilled that confirmed that the use of psychoactive drugs during interrogation was a long-standing practice.[33][34] Captives and former captives had been reporting medical staff collaborating with interrogators to drug captives with powerful psychoactive drugs prior to interrogation since the very first captives release.[35][36] In May 2003 recently released Pakistani captive Sha Mohammed Alikhel described the routine use of psychoactive drugs. He said that Jihan Wali, a captive kept in a nearby cell, was rendered catatonic through the use of these drugs.[*citation needed*]

Additionally, militaries worldwide have used or are using various psychoactive drugs to improve performance of soldiers by suppressing hunger, increasing the ability to sustain effort without food, increasing and lengthening wakefulness and concentration, suppressing fear, reducing empathy, and improving reflexes and memory-recall among other things.[37][38]

The first documented case of a soldier overdosing on methamphetamine during combat, was the Finnish corporal Aimo Koivunen, a soldier who fought in the Winter War and the Continuation War.[39][40]

Route of administration

Psychoactive drugs are administered via oral ingestion as a tablet, capsule, powder, liquid, and beverage; via injection by subcutaneous, intramuscular, and intravenous route; via rectum by suppository and enema; and via inhalation by smoking, vaporizing, and snorting. The efficiency of each method of administration varies from drug to drug.[41]

The psychiatric drugs fluoxetine, quetiapine, and lorazepam are ingested orally in tablet or capsule form. Alcohol and caffeine are ingested in beverage form; nicotine and cannabis are smoked or vaporized; peyote and psilocybin mushrooms are ingested in botanical form or dried; and crystalline drugs such as cocaine and methamphetamine are usually inhaled or snorted.

Determinants of effects

The theory of dosage, set, and setting is a useful model in dealing with the effects of psychoactive substances, especially in a controlled therapeutic setting as well as in recreational use. Dr. Timothy Leary, based on his own experiences and systematic observations on psychedelics, developed this theory along with his colleagues Ralph Metzner, and Richard Alpert (Ram Dass) in the 1960s.[42]

Dosage

The first factor, dosage, has been a truism since ancient times, or at least since Paracelsus who said, "Dose makes the poison." Some compounds are beneficial or pleasurable when consumed in small amounts, but harmful, deadly, or evoke discomfort in higher doses.

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Set

The set is the internal attitudes and constitution of the person, including their expectations, wishes, fears, and sensitivity to the drug. This factor is especially important for the hallucinogens, which have the ability to make conscious experiences out of the unconscious. In traditional cultures, set is shaped primarily by the worldview, health and genetic characteristics that all the members of the culture share.

Setting

The third aspect is setting, which pertains to the surroundings, the place, and the time in which the experiences transpire.

This theory clearly states that the effects are equally the result of chemical, pharmacological, psychological, and physical influences. The model that Timothy Leary proposed applied to the psychedelics, although it also applies to other psychoactives.[43]

Effects

Illustration of the major elements of neurotransmission. Depending on its method of action, a psychoactive substance may block the receptors on the post-synaptic neuron (dendrite), or block reuptake or affect neurotransmitter synthesis in the pre-synaptic neuron (axon).

Psychoactive drugs operate by temporarily affecting a person's neurochemistry, which in turn causes changes in a person's mood, cognition, perception and behavior. There are many ways in which psychoactive drugs can affect the brain. Each drug has a specific action on one or more neurotransmitter or neuroreceptor in the brain.

Drugs that increase activity in particular neurotransmitter systems are called agonists. They act by increasing the synthesis of one or more neurotransmitters, by reducing its reuptake from the synapses, or by mimicking the action by binding directly to the postsynaptic receptor. Drugs that reduce neurotransmitter activity are called antagonists, and operate by interfering with synthesis or blocking postsynaptic receptors so that neurotransmitters cannot bind to them.[44]

Exposure to a psychoactive substance can cause changes in the structure and functioning of neurons, as the nervous system tries to re-establish the homeostasis disrupted by the presence of the drug (see also, neuroplasticity). Exposure to antagonists for a particular neurotransmitter can increase the number of receptors for that neurotransmitter or the receptors themselves may become more responsive to neurotransmitters; this is called sensitization. Conversely, overstimulation of receptors for a particular neurotransmitter may cause a decrease in both number and sensitivity of these receptors, a process called desensitization or tolerance. Sensitization and desensitization are more likely to occur with long-term exposure, although they may occur after only a single exposure. These processes are thought to play a role in drug dependence and addiction.[45] Physical dependence on antidepressants or anxiolytics may result in worse depression or anxiety, respectively, as withdrawal symptoms. Unfortunately, because clinical depression (also called major depressive disorder) is often referred to simply as depression, antidepressants are often requested by and prescribed for patients who are depressed, but not clinically depressed.

Comparison of the perceived harm for various psychoactive drugs from a poll among medical psychiatrists specialized in addiction treatment (David Nutt et al. 2007)[59]

Psychoactive drugs are often associated with addiction or drug dependence. Dependence can be divided into two types: psychological dependence, by which a user experiences negative psychological or emotional withdrawal symptoms (e.g., depression) and physical dependence, by which a user must use a drug to avoid physically uncomfortable or even medically harmful physical withdrawal symptoms.[60] Drugs that are both rewarding and reinforcing are addictive; these properties of a drug are mediated through activation of the mesolimbic dopamine pathway, particularly the nucleus accumbens. Not all addictive drugs are associated with physical dependence, e.g., amphetamine, and not all drugs that produce physical dependence are addictive drugs, e.g., caffeine.

Many professionals, self-help groups, and businesses specialize in drug rehabilitation, with varying degrees of success, and many parents attempt to influence the actions and choices of their children regarding psychoactives.[61]

Common forms of rehabilitation include psychotherapy, support groups and pharmacotherapy, which uses psychoactive substances to reduce cravings and physiological withdrawal symptoms while a user is going through detox. Methadone, itself an opioid and a psychoactive substance, is a common treatment for heroin addiction, as is another

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opioid, buprenorphine. Recent research on addiction has shown some promise in using psychedelics such as ibogaine to treat and even cure drug addictions, although this has yet to become a widely accepted practice.[62][63]

The legality of psychoactive drugs has been controversial through most of *recent* history; the Second Opium War and Prohibition are two historical examples of legal controversy surrounding psychoactive drugs. However, in recent years, the most influential document regarding the legality of psychoactive drugs is the Single Convention on Narcotic Drugs, an international treaty signed in 1961 as an Act of the United Nations. Signed by 73 nations including the United States, the USSR, Pakistan, India, and the United Kingdom, the Single Convention on Narcotic Drugs established Schedules for the legality of each drug and laid out an international agreement to fight addiction to recreational drugs by combatting the sale, trafficking, and use of scheduled drugs.[64] All countries that signed the treaty passed laws to implement these rules within their borders. However, some countries that signed the Single Convention on Narcotic Drugs, such as the Netherlands, are more lenient with their enforcement of these laws.[65]

In the United States, the Food and Drug Administration (FDA) has authority over all drugs, including psychoactive drugs. The FDA regulates which psychoactive drugs are over the counter and which are only available with a prescription.[66] However, certain psychoactive drugs, like alcohol, tobacco, and drugs listed in the Single Convention on Narcotic Drugs are subject to criminal laws. The Controlled Substances Act of 1970 regulates the recreational drugs outlined in the Single Convention on Narcotic Drugs.[67] Alcohol is regulated by state governments, but the federal National Minimum Drinking Age Act penalizes states for not following a national drinking age.[68] Tobacco is also regulated by all fifty state governments.[69] Most people accept such restrictions and prohibitions of certain drugs, especially the "hard" drugs, which are illegal in most countries.[70][71][72]

In the medical context, psychoactive drugs as a treatment for illness is widespread and generally accepted. Little controversy exists concerning over the counter psychoactive medications in antiemetics and antitussives. Psychoactive drugs are commonly prescribed to patients with psychiatric disorders. However, certain critics[*who?*] believe that certain prescription psychoactives, such as antidepressants and stimulants, are overprescribed and threaten patients' judgement and autonomy.[73][74]

Effect on animals

A number of animals consume different psychoactive plants, animals, berries and even fermented fruit, becoming intoxicated. An example of this is cats after consuming catnip. Traditional legends of sacred plants often contain references to animals that introduced humankind to their use.[75] Animals and psychoactive plants appear to have co-evolved, possibly explaining why these chemicals and their receptors exist within the nervous system.[76]

Widely used psychoactive drugs

This is a list of commonly used drugs that contain psychoactive ingredients. Please note that the following lists contains legal and illegal drugs (based on the country's laws).

- Alcohol
- Benzodiazepines
- Caffeine
- Cannabis
- Cocaine
- Heroin
- LSD
- Methamphetamine
- Ecstasy
- Nicotine
- Opioids
- Psilocybin mushrooms

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