

Essential Concepts

- Most psychiatrists practice non-Hippocratically.
- The Hippocratic approach to medicine is not simply an ethical viewpoint but rather a philosophy of disease.
- In that philosophy, disease is natural, and cure also comes from nature. The physician's role is to help nature along or to get out of the way.
- Diseases are self-limiting, curable, or incurable. The first and third types should not be treated; the second should. Distinguishing between the three is the art of medicine.
- Symptom-oriented treatment, with aggressive use of medications, goes against this Hippocratic philosophy; this is the current approach in psychopharmacology.
- Hippocratic psychopharmacology is based on two rules: Holmes' rule states, "All medications are guilty until proven innocent". Osler's rule states, "Treat diseases, not symptoms."
- I argue that unless we follow these two rules, we do more harm than good.

PRINCIPLES OF PSYCHOPHARMACOLOGY: IMPLICATIONS OF A HIPPOCRATIC APPROACH

The great father of modern medicine, William Osler, advised his students: "Read the journals and the old books." The journals keep us up-to-date on recent research; the old books give us perspective and provide universal principles.

The principles of psychopharmacology follow from the principles of medicine, among which the Hippocratic approach is

one perspective, oft-quoted but frequently misunderstood. Hippocrates' view of medicine, in contrast to other schools, was that disease comes from nature: It is not unnatural. Thus it is not something to fight against but rather a natural process that nature itself can heal. The job of the physician is to help guide nature toward health, using measures such as diet and exercise, rather than to engage in combat with nature through medicines and toxins. Thus the key Hippocratic idea is that nature heals, and the doctor is only the "handmaiden" to nature. Nature cures; the doctor assists.

Many, if not most, illnesses improve naturally, and our role is to not get in the way of nature but to help nature along. Hence the Hippocratics divided diseases into the self-limited, the treatable, and the incurable. In the first and third cases, treatments in general are unnecessary and often harmful; in the second case, they are needed. The art of medicine is to distinguish between these three cases.

Thus the famous Hippocratic maxim of "First do no harm" is not an abstract ethical ideal; rather, it grows out of this basic philosophy of disease.

It is my view that most psychiatrists practice non-Hippocratically. We think that we need to treat everyone who enters the doors of our offices. There is precedent for this view in the founder of American Psychiatry, Benjamin Rush, who directly attacked the Hippocratic philosophy of treatment and who was a strong advocate of active intervention to treat all kinds of illnesses, including mental illness, mainly through bleeding. The Hippocratic approach was long forgotten in the Middle Ages and into the modern era. In the United States, the Hippocratic philosophy was resurrected in the late nineteenth century by Oliver Wendell Holmes and William Osler.

Based on their writings, I have derived two rules that should help clinicians to engage in Hippocratic psychopharmacology (Table 5.1).

Holmes' Rule

The first rule is derived from the physician and writer Holmes, who said in 1861:

TABLE 5.1. Rules for a Hippocratic Psychopharmacology

Holmes' rule: Medications are guilty until proven innocent.

Osler's rule: Treat diseases, not symptoms.

Presumptions are of vast importance in medicine, as in law. A man is presumed innocent until he is proved guilty. A medicine . . . should always be presumed to be hurtful. It always is directly hurtful; it may sometimes be indirectly beneficial. If this presumption were established . . . we should not so frequently hear . . . that, on the whole, more harm than good is done with medication. Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out a few specifics which our art did not discover, and is hardly needed to apply; throw out wine, which is a food, and the vapors which produce the miracle of anesthesia, and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.

Thus Holmes' rule is that there must be empirical proof that a treatment is effective so as to outweigh the presumption against the use of a medication. If clinicians followed this rule, they would avoid treatment with medications whose efficacy has not been proven at least to some degree. As Osler put it, all medications are toxic; it is only the indication and the dosing that makes them effective. Thus, before using any medication, we must presume harm; the burden of proof is on the medication to be shown effective, not on anyone to show that the medication is not harmful. Our risk-benefit calculations should begin not on the risk side but on the benefit side. Otherwise, we end up with a kind of "gabapentin syndrome"—giving people safe, though ineffective, drugs (or alternatively, widely using drugs effective only for a few conditions).

For example, in the case of antidepressants for bipolar disorder, clinicians have been breaking Holmes' rule egregiously. We have engaged in the extensive long-term use of antidepressants despite two decades of randomized maintenance data demonstrating that they are ineffective, on the whole, in the prevention of depressive episodes in bipolar disorder. Recent data are supporting this view even with newer-generation antidepressants.

I am surprised how often clinicians tell me that they want more evidence to *stop* using antidepressants. If they were practicing Hippocratic medicine and following Holmes' rule, they would want evidence to *start* using medications, not to stop them. The burden of proof is not that medications

should be used unless proven ineffective and unsafe but that they should *not* be used unless proven effective and safe. With antidepressants, for some reason, we have gotten it backwards.

Osler's Rule

The second rule is derived from the father of modern medicine, William Osler, who urged in 1895:

A man cannot become a competent surgeon without a full knowledge of human anatomy and physiology, and the physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practising a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.

Osler emphasized that we need to learn first about diseases before we can really do much about treatment. Thus Osler's rule is that we should treat syndromes (based on underlying diseases), not symptoms. Symptoms are not what need to be treated; they are signs that point to the disease (or diagnosis), which is what needs to be identified and treated. If clinicians followed this rule, they would avoid using drugs for multiple symptoms, which leads to a haphazard polypharmacy. Thus, in treating bipolar disorder, patients often receive antidepressants for depressive symptoms, antipsychotics for manic symptoms, anxiolytics for anxiety symptoms, sedatives for insomnia, and mood stabilizers for mood swings. This symptom-oriented approach to treatment is prescientific rather than scientific, nineteenth-century-based rather than up to date, and anti-Hippocratic. The Oslerian approach would be to focus on the diagnosis (not the symptoms), which is bipolar disorder, and emphasize mood stabilizers, as much as possible by themselves, as the only class of treatment that treats the whole illness (acute depression, acute mania, and prophylaxis of mood episodes). In cases where the disease is not well identified, or where perhaps no disease exists, then treatment is symptomatic, of a Band-Aid nature, and the risk-benefit ratio for medication treatment would become more unfavorable to extensive prescription of such treatments. Such is not the case with bipolar disorder, however, a diagnosis that has been well described since the Roman physician Arateus of Cappadocia (second century A.D.) and whose biological basis is reasonably well established.

This need not mean that we should never use medications merely to relieve symptoms. It does mean that this approach goes against the Hippocratic view of medicine, and we should take it only in the short term, reluctantly, and for immediate relief of symptoms. In psychiatric populations, where diseases are poorly understood (as in children and the elderly), and there is rampant symptomatic polypharmacy. And many psychiatrists consider this state of affairs to be acceptable. Osler's rule would give us pause.

SUMMARY

To paraphrase the great German psychiatrist, Karl Jaspers (who in my view is a much greater thinker for psychiatry than either Sigmund Freud or Emil Kraepelin), most of our mistakes and disagreements stem from our beliefs and concepts rather than from science or research. Readers who have picked up this book to better diagnose or treat mood disorders will not gain much benefit unless they first think about their conceptual assumptions about psychiatric treatment. In the past, we avoided medications too much: Psychoanalysis was seen as the solution. Now, I believe that we use medications too much: We practice a symptom-oriented psychopharmacology that belongs in the nineteenth century. We need to be clear about what we need to do: We should prescribe medications primarily for diseases, not for symptoms, and not even for all diseases; we should avoid prescribing them by habit, only doing so when proof of benefit exists and far outweighs risks. With this basic philosophy, we can then turn to studies and research and data, leading to a scientific Hippocratic psychopharmacology. Otherwise, in my view, the science and the data will be twisted by doctors and patients to their own whims, producing that eclectic mishmash that is contemporary psychiatry.

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Genes and Environment

Essential Concepts

- There are roughly equal genetic and environmental causes for mood disorders.
- The genetic part consists of polygenic susceptibility to illness rather than Mendelian inheritance.
- The environmental part consists of specific life events, which mainly serve to trigger individual episodes.

I will discuss the etiology of mood disorders in two major categories: genetics and environment.

GENETICS

Numerous years of research have failed to find a single gene or a few genes that "cause" mood disorders (or psychotic disorders). This is likely the case because most psychiatric conditions are not analogous to classic Mendelian illnesses. In Mendelian genetics, qualitative changes occur with often a single-gene change. Thus, if a gene is dominant, it produces a certain trait. If a gene is recessive, it produces a certain trait in the homozygous mode (two recessive genes occurring together), meaning one-fourth of the time. These occurrences are predictable. This type of genetics accounts for many inherited diseases in which the environment plays little to no role. However, many common chronic medical illnesses do not follow this pattern of inheritance. For instance, we know that hypertension and diabetes mellitus (type II) have heritable aspects, yet they are neither autosomal dominant nor recessive in their frequency patterns. Similarly, normal physical features, such as height or weight or intelligence, are inherited, but not in an autosomal manner. Instead, with such chronic illness or such physical features, what seems to be inherited is a tendency to have more or less susceptibility to those conditions or features. These kinds of genetic effects are quantitative rather than qualitative. A single gene has relatively little effect, and it appears