PART I General Principles
Core Concepts of Good Psychopharmacology

It is a capital mistake to theorize before you have all the evidence. It biases the judgment.

- Sir Arthur Conan Doyle

CAUSE AND EFFECT

When someone takes a medication for depression, anxiety, or any other psychiatric problem, how do they or the prescriber know for certain if they are actually better or worse? And in either instance, whether to credit (or blame) the drug? If depression gets better 4–6 weeks after taking an antidepressant, how confidently should we attribute improvement to the drug rather than to serendipity? What if the patient gets better only after 14–16 weeks – is that too far in time to distinguish a plausible drug effect from spontaneous remission? Or, when can we assume the outcome was still a likely drug effect, given that an adequate trial may take longer in some people than others? If they felt better in just a few days, is that evidence of a placebo effect? Or, if they became suicidal or agitated, how do we know if that reflects an adverse drug effect or simply a worsening due to the natural course of illness?

Cause-and-effect relationships are often presumed throughout medicine, even though drugs can have unpredictable effects and despite the fact that numerous biological, psychological, and environmental factors contribute to outcomes. Causality is all the more difficult to infer when a patient receives more than one treatment (as occurs not infrequently in real-world practice), or other psychoactive factors complicate the picture (such as alcohol or drug abuse, or sleep deprivation, or life catastrophes). How do we account for subjective versus objective signs of improvement, while considering the effects of time alone, placebo and nocebo effects, the therapeutic alliance, variable pharmacodynamic drug effects, pharmacokinetic interactions, comorbidities, dosing effects, and – not of least importance – whether the prescribed treatment is even appropriate to the presenting ailment?

Psychiatric drug effects are remarkably varied and unreliable. Contrast the poorly predictable outcome of giving someone a selective serotonin reuptake inhibitor (SSRI) for depression versus the relative certainty of administering general anesthesia for surgery. No anesthesiologist ever tells their patient they have about a 6 in 10 chance that the medication they are about to receive will make them go to sleep. Admittedly, the sleep-inducing effects of halothane produce a safer and more reliable result than having the patient inhale an ether-soaked rag (and halothane is no picnic if the patient has an unrecognized susceptibility to malignant hyperthermia). But can psychotropic drugs ever deliver the same kind of causal precision and reliability for producing an intended effect as occurs with anesthesia induction?
Causal inferences are vulnerable to the so-called post hoc ergo propter hoc or logical fallacy phenomenon, in which one concludes that whatever happens after a temporal sequence of events (e.g., taking a medication and then feeling better or worse) necessarily reflects cause and effect. The hazards of spurious associations and outright superstitions abound in psychopharmacology, where both doctor and patient perceptions about cognitive and emotional processing are colored by pre-existing beliefs and expectations. More scientifically, causal relationships in medicine are sometimes judged according to criteria such as those described by Hill (1965), as summarized in Box 1.1.

Additionally, one must consider the presence of confounding factors or potential biases (e.g., different susceptibilities or degrees of responsibility/nonresponsivity across individuals – as when antibiotics may be less effective in someone who is immunosuppressed, or poorly adherent, or has a superinfection), and the impact of other simultaneous interventions that could interact and alter efficacy or tolerability.

Observed Outcomes
Prescribers and patients do not necessarily look for the same tangible results when judging pharmacotherapy effects. For example, surveys show that depressed patients’ main therapeutic goals are to feel that life is meaningful and enjoyable, and to feel satisfied with themselves. Doctors, by contrast, set out to eliminate negative feelings such as depression, despair, or hopelessness, and help patients regain interest or pleasure from doing things. These differences may seem nuanced, and could just be a matter of semantics, but they set the stage for how success gets measured, and what kinds of expectations all parties bring when a psychopharmacotherapy is undertaken.

Knowingly or otherwise, clinicians who prescribe psychotropic medications must consider a multitude of factors, both biological and nonbiological, for judging drug effects; and, before that, deciding what, when, how, and for whom to prescribe any agent. Good psychopharmacology reflects such an awareness, and at its best, carries as prerequisite a systematic diagnostic assessment, appreciation for relevant dimensions of psychopathology, and the “fit” between symptom profiles and pharmacodynamic properties, as well as economy of scale (as when one drug accomplishes more than one goal), avoidance of redundant or unnecessary or ineffective agents, and ultimately, customer satisfaction.

Consider the fit between prescribed medications and clinical phenomenology in Clinical Vignette 1.1. James’s case illustrates the kind of litany of problems that often afflict real-world patients. First, one must filter a plethora of psychiatric phenomena ranging from trouble with mood and anxiety to illicit substances to...
James was a 24-year-old information technologist who carried diagnoses of bipolar disorder, attention deficit disorder (ADD), stimulant (cocaïne) use disorder, cannabis use disorder, non-verbal learning disability, generalized anxiety disorder, and a mixed personality disorder involving narcissistic and histrionic traits. His extensive medication history has included a multitude of drugs from virtually all major classes and combinations over the years, including anticonvulsants, antidepressants, antipsychotics, benzodiazepines, and psychostimulants. During his most recent consultation, the psychiatrist whom he saw reviewed his lengthy medication history, sought to identify which medications he had never taken, and picked lithium largely because it was one of the few medications James had never tried. He now presents for follow-up noting that “the lithium isn’t working.”

Corroborative information, although their input too may require filtration and their face value cannot necessarily be taken for granted (as when judging the biases of an estranged, resentful, or otherwise dissatisfied partner or other family member). In James’s case, declaring lithium a “failure” assumes that his ailment – the object of treatment – conforms to a symptom picture for which lithium renders a known benefit (such as lithium-responsive bipolar disorder, or at least, impulsive aggression, or suicidal behavior) – lest its selection reflect merely an otherwise random choice based on the hearsay of previous diagnoses that may or may not be correct.

**Definition**

*Form fruste* conditions refer to clinical presentations in which only some of the defining elements of a disease state are evident. (More on this in Chapter 2.)

**Clinical Tells**

Clinical powers of observation are as vital to psychopharmacology as to any other area of medicine. One would be remiss not to notice exophthalmos and a bulging lower neck in someone complaining of depressed mood and fatigue, or impoverished or concrete thinking...
(schizophrenia? traumatic brain injury? low intellectual functioning? cultural unfamiliarity?), or lack of eye contact, stereotypies, verbosity, mood-incongruent affect, perseveration or difficulty shifting sets, and mismatches between objective functioning and subjective complaints. Such observable clues are the stock-in-trade of CSI psychiatry, juxtaposed alongside a patient’s subjective self-report. Only after one formulates a clear impression of the true nature of the problem can one speak of choosing from among the most appropriate treatments, and then gauging the likelihood that the “right” intervention will yield the desired result.

**Tip**
Discordant match-ups between objective signs and subjective symptoms signal diagnostic complexity.

### DECIDING WHEN PHARMACOTHERAPY IS INDICATED

The sheer making of a psychiatric diagnosis does not necessarily or automatically equate to an indication for pharmacotherapy. Judgments in this area typically hinge not only on severity of symptoms, but also the degree to which symptoms cause distress or disrupt functioning, or the presence of certain cardinal symptoms (such as frank psychosis or severe agitation). An implicit assumption is that effective pharmacotherapy exerts a larger effect than that of a placebo. Just as it makes no sense to initiate or continue a medication that yields no discernible benefits, so too should a proposed pharmacotherapy target symptoms unambiguously, and with reasonable expectations for diminishing their intensity if not eradicating them altogether. And the only way to choose purposeful treatments that most reliably fit the bill, short of blind luck, is to base treatment decisions on known outcomes from well-conceived and executed clinical trials in well-characterized patient groups – that is, drawing upon an empirical evidence base.

### EVIDENCE-BASED PSYCHOPHARMACOLOGY

Evidence-based medicine (EBM) simply means having a foundation for choosing among reasonable treatment options, supported by some degree of empirical proof. Large, randomized placebo-controlled trials are generally considered to be the gold standard for judging rigor behind an evidence base, because they provide sufficient statistical power to differentiate a real effect (or lack of an effect) from a random fluke, and to capture differences that are both statistically and clinically meaningful, even if the magnitude of those differences is subtle. However, as noted in an early editorial describing EBM by Sackett and colleagues (1996, p. 72), “Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions.” In other words, even if just a single patient has an extremely favorable outcome from well-conceived and executed clinical trials, that observation alone constitutes evidence of efficacy – *for that one patient*. The problem comes if one tries to generalize about that singular result to other patients with a broader basis.
The Course of Treatment

Once a medication that befits a clinical symptom profile has been chosen and begun, how does one decide what comes next? On what timescale is progress reasonably tracked, and how is it quantified? Short of intuition, what parameters help guide decisions about whether dosage adjustments should be made, and when? At what point might additional pharmacotherapies be appropriate? And, when can meaningful conclusions be drawn about the likelihood of seeing further drug effects – that is, when to decide if a drug trial is ineffective or partially effective, and whether to discontinue it, replace it, or retain and augment it?

Circumstances that influence the above considerations vary from ailment to ailment, as well as from drug to drug. Some agents have identified target doses or dosing ranges, and may require titration schedules that are often limited by safety or tolerability issues. Other medications can essentially be “loaded” or dosed rapidly from the outset without jeopardizing tolerability, and possibly leading to a faster onset of efficacy.

As a rule of thumb, adequate medication trials usually take longer and may often involve higher doses in chronic, highly recurrent, or otherwise complex conditions, as compared to relatively “simpler” presentations with less entrenched and enduring stigmata of an underlying disorder. Symptoms that are ego-alien may be easier to dislodge than those which become more engrained or are fundamentally consistent with a patient’s basic view of himself and the world. Here, concepts involving personality traits, core beliefs, and
self-image, as described further in Chapter 2, can color how any given patient uniquely presents with a “generic” disorder of mood, anxiety, behavior, or cognition; such overtones bear on course and prognosis, as well as distinctions between the more-likely viable targets of pharmacotherapy (such as vegetative signs, or poor impulse control, or panic attacks) from those that are less-likely viable (such as poor distress tolerance or coping skills, general mistrust of others, long-standing feelings of injustice or envy, or emotional dysregulation linked to interpersonal sensitivities).

THE TWO-WEEK/20% RULE

While different mental health disorders vary greatly in their features and treatment response, and the trajectory of pharmacotherapy outcomes can vary by patient-specific factors (such as severity, chronicity, pharmacokinetics (e.g., ultrarapid metabolizer phenotypes) and degree of previous treatment resistance), it is nevertheless reasonable to consider the two-week mark as perhaps the first decision-making milestone in the time course for judging a drug’s effect on a major psychiatric condition. Responses within one week or sooner generally raise suspicions about transient placebo effects, albeit with some exceptions (notably, rapid antidepressant response to intravenous ketamine); steady-state pharmacokinetics often are not achieved until 5–14 days with many psychotropic medications across classes, making sooner attributions less reliable.

Several lines of evidence suggest that by two weeks, at least minimal improvement – visible like the sprouting of a seedling, and quantifiable by at least a 20% improvement in symptom severity from baseline – predicts subsequent stable response or remission, at least in the cases of major depression (Papakostas et al., 2006; Szegedi et al., 2009), bipolar depression (Kemp et al., 2011), schizophrenia (Leucht et al., 2007; Samara et al., 2015), panic disorder (Pollack et al., 2002), and generalized anxiety disorder (Rynn et al., 2006). There are conflicting findings about whether signs of improvement in just the first week more likely reflect placebo than pharmacodynamic effects, particularly in light of concerns that early placebo effects can be transient. (Hence the basis for single-blind one-week placebo lead-in periods in clinical trials striving to minimize placebo responsivity.) Further complicating debates over possible placebo transience in early responders is the notion of an additive effect between initial placebo-responsiveness and subsequent pharmacodynamic efficacy; in other words, placebo- and drug-response may not be mutually exclusive phenomena during treatment with an active psychotropic agent, and it is possible at least in some instances that even if a brisk initial improvement did reflect a placebo mechanism, that phenomenon does not prohibit subsequent and more enduring pharmacodynamic efficacy from the actual drug. Said differently, across multiple disorders there is a high negative predictive value for lack of minimal response in the first two weeks; absence of detectable signs of improvement in that time therefore makes it advisable to alter an existing treatment regimen in some way (via dosing changes, augmentations, or substitutions).

Tweaking

There has been remarkably little study to examine when and how clinicians decide to alter an existing drug regimen. In formal clinical trials, decision points are sometimes algorithmic: if a milestone for improvement is not met by a certain timepoint, adjustments may be protocol-driven (usually dosage increases; sometimes measurement of serum drug levels or reassessment of confounders such as poor adherence or illicit substance use). In real-world practice, rules are looser, seldom evidence-based, and often nonexistent for deciding if and when to alter a drug dose or stop or start a medication. Occasionally, titration schedules are dictated by a drug manufacturer, if not by scientific rationale, for a particular treatment. For example:

- lamotrigine upward dosing in bipolar disorder (see Chapter 13);
- oral loading of divalproex (20–30 mg/kg) in acute mania may yield a faster onset of symptom resolution than more gradual dose escalations, balanced against tolerability (chiefly, gastrointestinal (GI) upset);
- there is little rationale, barring toxicity, for changing lithium doses based on serum lithium levels before the elapse of five days since the last dosage change (i.e., five half-lives to reach steady-state);
- carbamazepine may require up-dosing within several weeks of its initiation due to autoinduction of its metabolism;
The Two-week/20% Rule

• oral loading of divalproex (20–30 mg/kg in divided doses) may hasten antimanic response (see Chapter 13);
• a rapid initial dose escalation with olanzapine may yield more rapid and effective treatment for acute agitation as compared to a more usual gradual dosing schedule, with comparable tolerability;
• someone with a known ultra-rapid metabolizer genotype for a pertinent catabolic enzyme (see Chapter 8) may expectably require higher than usual doses (though usually without precise compensatory adjustment).

When should dosing adjustments logically be made, short of predetermined dose-titration schedules? There may not always be a “should” to answer this question, given high interindividual variability in drug response. One guiding principle involves responding to trends rather than transient vicissitudes in symptom status, not unlike following the stock market. Certainly, when unambiguous and sustained dips or plateaus are reached and adverse effects are minimal and tolerable, it is reasonable to consider dose changes. At the same time, one must be aware that some agents likely have pharmacodynamic benefits as well as adverse effects. For example, as is also the case for bupropion. Lower rather than higher doses of some medications (such as some second-generation antipsychotics (SGAs)) may yield better outcomes in certain subpopulations (e.g., anxious depressed patients), as discussed in Chapter 13.

Newtonian Psychopharmacology

To paraphrase Newton’s first law of motion, the trajectory of response to a psychotropic drug will likely remain in constant motion unless acted upon by an outside force. (Outside forces might include nonadherence, substance misuse, medical comorbidities, or worsening of the natural course of illness.) Generally speaking, improvement from an episode of depression, mania, or psychosis follows a time course for recovery that, while not entirely predictable, follows a fairly constant path. Once an appropriate dose has been achieved and signs of improvement are evident, there is often no rationale to tweak a dose so long as signs of improvement do not plateau and tolerability issues are minimal. Overwatering a plant does not make it grow faster. Supratherapeutic drug dosing before an adequate trial has elapsed also generally has little rationale and may be either unnecessary or counterproductive (as in the case of rapid neuroleptization with first-generation antipsychotics (FGAs) producing acute dystonia), with just a few exceptions:

• rapid dosing of antipsychotic drugs, particular those with strong D2 binding affinity, increases the risk for dystonic and other serious adverse motor reactions;
• expected “target” doses may vary from person to person for a wide variety of reasons, limiting the extent to which inexorable dose escalations may be necessary or wise.

Not surprisingly, in a large clinical trial involving expert care for bipolar disorder, eventual treatment responders had fewer necessary clinical adjustments (“NCAs”) made to their treatment regimens than did eventual nonresponders; every NCA statistically decreased eventual response status by 30% (Reilly-Harrington et al., 2016). Relatedly, every one-unit increase (i.e., worsening) in a patient’s Clinical Global Impressions (CGI) overall severity score was associated with a 13% increase in the likelihood of incurring an NCA (Reilly-Harrington et al., 2013). Of course, correlations between multiple NCAs and poorer outcome may simply be a proxy marker for illness complexity, drug tolerability, or poor prognosis in general, while more straightforward clinical presentations may simply require adjustments to a drug regimen less often.

Dosing: Usual, Homeopathic, Supratherapeutic

There has been surprisingly little formal literature examining the many assumptions clinicians make about dose–response relationships with respect to pharmacodynamic benefits as well as adverse effects. Some of the pertinent questions in this realm for which empirical data are either indirect or limited include:

• If a patient appears to improve on a medication at a lower-than-usual dose, is it unwise to maintain the low dose rather than strive toward usual dosing regardless of apparent improvement in baseline symptoms?
The ability to maintain a sense of mental equilibrium in the face of adversity is, the ability to maintain a sense of equilibrium and relative freedom from psychiatric symptoms in the face of adversity.

The ability to maintain a sense of mental equilibrium when under stress is in some ways analogous to the function of a gyroscope keeping an airplane level during flight, regardless of weather conditions that might otherwise jeopardize its aeronautical integrity. For an expanded depiction of this concept, see Box 1.2.

**Psychiatric Gyroscopes**

The concept of resilience in mental health is rather analogous to the role of a gyroscope in maintaining a level, unswerving flight path for aircraft regardless of encountered turbulence. Whatever psychiatric shearing forces the winds of fate may inflict, we rely on an intact internal guidance system to maintain composure and a sense of forward movement without veering too far off path. Effective psychiatric treatments ought not to simply reduce current symptoms or prevent relapses, but even more critically, help ensure an intact capacity to compensate mentally for normal stresses.

Symptom checklists and rating scales are useful for gauging the impact of symptoms on how a patient navigates everyday stresses. Life itself is a psychiatric stress test, akin to the treadmill used to assess myocardial function. Or, taking an automotive analogy, no matter how appealing and pristine a vehicle looks in the showroom, one cannot really know how well it performs until one takes it on the road and puts it through its paces. In the world of mental health, stressful life events are like the everyday potholes and maneuverings that cars endure when being road-tested. If a psychotropic drug is successful in reducing psychiatric symptoms, we learn far more about the breadth and durability of its effect by asking how it helps improve the patient's everyday functioning and capacity for resilience when under pressure – that is, the ability to maintain a sense of equilibrium and relative freedom from psychiatric symptoms in the face of adversity.

**Box 1.2**

### JUDGING TREATMENT EFFECTS: IS THE PATIENT REALLY BETTER?

Symptom checklists and rating scales are useful for judging the presence and severity of a disease state at a given time, but they are not as dynamically informative as gauging the impact of symptoms on how a patient navigates everyday stresses. Life itself is a psychiatric stress test, akin to the treadmill used to assess myocardial function. Or, taking an automotive analogy, no matter how appealing and pristine a vehicle looks in the showroom, one cannot really know how well it performs until one takes it on the road and puts it through its paces. In the world of mental health, stressful life events are like the everyday potholes and maneuverings that cars endure when being road-tested. If a psychotropic drug is successful in reducing psychiatric symptoms, we learn far more about the breadth and durability of its effect by asking how it helps improve the patient's everyday functioning and capacity for resilience when under pressure – that is, the ability to maintain a sense of equilibrium and relative freedom from psychiatric symptoms in the face of adversity.

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Of course, another way to determine empirically if the patient “really is better” after an adequate trial has elapsed is to stop the treatment in question to find out if clinical symptoms then recur or worsen. The obvious downside to this approach is its risk for clinical deterioration, with no guarantees against further declines if the stopped therapy is restarted. Sometimes this approach can be helpful for giving patients (or practitioners) a more unequivocal appraisal of the effects of a drug whose efficacy and purpose may have thus far been ambiguous.