PART I General Principles

1 Core Concepts of Good Psychopharmacology

LEARNING OBJECTIVES

- [ ] Recognize cause-and-effect relationships in psychopharmacology
- [ ] Adopt an investigative "forensic" mindset to assess psychopathology and match symptom constellations to the best-fitting treatment
- [ ] Recognize levels of empirical evidence that support any given pharmacotherapy intervention before making conclusions about generalizability or likelihood of a meaningful effect
- [ ] Know appropriate benchmarks and timepoints for judging if and when to alter medication dosages or otherwise adjust a treatment regimen
- [ ] Focus on putative drug mechanisms, underlying dysfunction of neural networks, and findings from empirical trials, rather than simply on whether or not a drug carries "on"- or "off"-label regulatory agency approval
- [ ] Always strive to define as clearly as possible the intended symptom targets of any treatment

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

– Sir Arthur Conan Doyle

A 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.

Tip

Just because an effect temporally follows an intervention does not necessarily demonstrate a cause-and-effect relationship.

Additionally, one must consider the presence of confounding factors or potential biases (e.g., different susceptibilities or degrees of responsivity/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

Box 1.1

Bradford Hill Criteria for Judging Cause and Effect

Criteria	Relevance
Strength of apparent association	Bigger associations = bigger effects
Consistency (reproducibility)	Consistent findings across settings = more likely a true association
Specificity	Specific population with specific disease, unlikely other explanations
Temporality	Exposure precedes outcome
Dose effect	Greater exposure imparts greater risk (but, there could also be a necessary threshold level of exposure)
Plausibility	Is there a plausible pharmacological mechanism?
Coherence	An explanation for likely association makes sense given existing knowledge
Experiment	Experimental interventions can alter the conditions
Alternate explanations	Do other likely explanations exist for the observed association?

CLINICAL VIGNETTE 1.1

James was a 24-year-old information technologist who carried diagnoses of bipolar disorder, attention deficit disorder (ADD), stimulant (cocaine) use disorder, cannabis use disorder, nonverbal 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."

cognitive complaints, all colored by suspected personality characteristics; then, a vast historical pharmacopoeia requires a better understanding – what medications, at what doses, for how long, with what intended symptom targets, and with what observed effects? And, how accurate is the subjective recall of those parameters? Patients with multiple diagnoses pose especially difficult challenges, not simply because of the need to parse transdiagnostic overlapping symptoms (such as inattention due to bipolar disorder versus ADHD, or apathy due to depression versus cannabis abuse), but also because clinical improvement may demand a hierarchical approach to treatment (e.g., detoxification and abstinence as prerequisites for identifying and targeting primary mood symptoms). Lastly, complex cases sometimes invite the strategy employed here of sifting through a lifetime medication history in order simply to find a drug previously untried that is remotely pertinent to any of the key complaints and/or presumptive diagnoses – followed by the dismay of yet another failure.

A logical and systematic approach to appropriate pharmacotherapy in this case, as in any, begins with a careful and sometimes painstaking reassessment of the presenting phenomena and their context, including the chronology of symptoms, their longitudinal course over time, a careful interview to establish the presence or absence of distinct symptom constellations, episodes versus "usual" states, and the criteria by which categorical diagnoses are formulated. Knowledgeable collateral historians are often helpful sources of 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.

B CLINICAL ASSESSMENT: CSI PSYCHIATRY

Good diagnosticians weave together signs and symptoms into a coherent narrative that fits a recognizable pattern. When we play psychiatric detective, diagnostic clues are like persons of interest in a crime scene investigation (CSI), leading us to develop working hypotheses about the most likely culprit(s). No clinician worth his or her salt can deny the thrill of discovery when medical sleuthing leads to the realization of a disease-defining symptom constellation. But when no clear-cut pattern is evident, sharp psychiatric detectives realize that absence and formulate an impression based on possible *form fruste* presentations, or dimensions of psychopathology that most closely approximate a categorically defined symptom profile. In either instance, appropriate treatments should conform to rigorous clinical appraisals the way a jury might consider whether or not there exists a preponderance of evidence, or even more rigorously, certainty beyond a reasonable doubt.

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.

C 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.

D 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 and enduring improvement with a medication, without any corroborative proof from other sources or outside studies, 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 Shortfall of Purely Observational Studies

A famous review in the British Medical Journal (BMJ) once noted that no randomized controlled trials (RCTs) have been conducted to prove that parachutes prevent death or major trauma during free fall from an airplane. The authors opined that "everyone might benefit" if ardent critics of purely observational studies devised and participated in such a double-blind, randomized crossover trial (Smith and Pell, 2003).

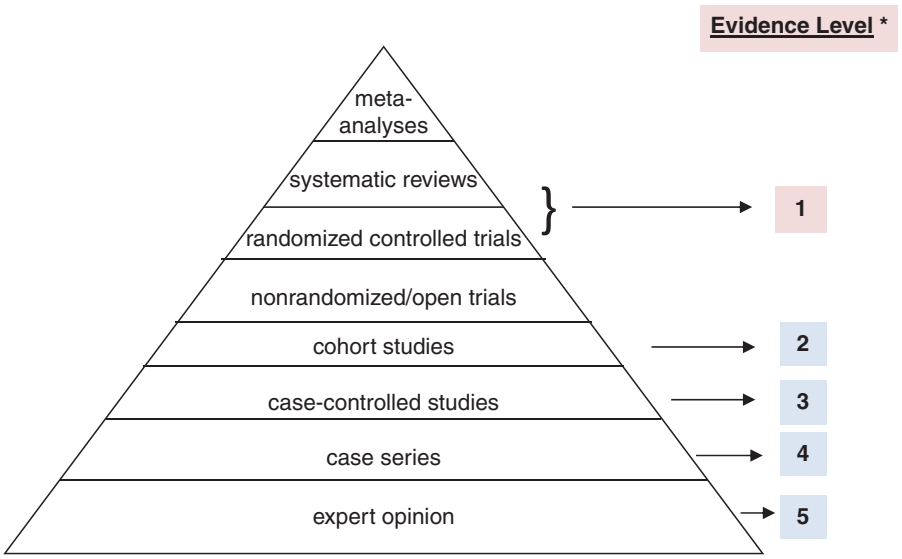
Traditionally, levels of evidence are described hierarchically, as shown in Figure 1.1.

Tip

Meta-analyses and large RCTs represent the most rigorous levels of evidence.

With this framework, one must distinguish the degree of rigor and generalizability (or relative lack thereof) of studies that have been undertaken – and the extent to which an existing database is more provisional or definitive. For example, small open case series or even small RCTs may be undertaken more as *proof-of-concept* studies intended to demonstrate feasibility or anticipate likely within-group effect sizes (as explained in Chapter 3), from which future, more definitive studies can be planned and executed. A small-scale provisional study of a novel compound that shows a significant improvement from baseline in a particular measure of psychopathology may be intended more to help frame the logistics of a larger RCT, rather than to inspire immediate uptake in routine clinical practice. Similarly, small studies that are not intentionally designed to test a hypothesis are sometimes

Figure 1.1 Levels of evidence in clinical trials.



* Oxford Centre for Evidence-based Medicine

referred to as *hypothesis-generating* – think of a manufacturer beta-testing several prototypes before devoting greater resources to final product development, or a film's producer showing previews that feature alternate endings to gauge audience response before deciding on the final cut.

Tip

Case reports and open trials serve more as hypothesis-generating than hypothesis-testing components of a treatment database. This means that they suggest ideas about viable therapies, rather than demonstrate that they are valid or reliable.

Relatedly, investigators in large RCTs sometimes undertake planned interim analyses to gauge the progress of an ongoing study – rather like peeking at a cake in the oven half way through the baking process, or sampling a stew before it is fully cooked simply to check whether the ingredients are coming together as intended. It would be quite the culinary gaffe to serve a half-baked meal to one's guests, just because an early sampling seemed promising.

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).

F 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.

Tip

A measurable improvement of at least 20% from baseline after two weeks of treatment may predict eventual robust response after an adequate trial has elapsed.

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;

- rapid dosing of antipsychotic drugs, particular those with strong D_2 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.

Tip

Beware, excessive tweaking of a drug regimen may itself be an outcome measure that serves as a clue about poor prognosis.

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.

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:

- 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).

Tip

Have a clear rationale in mind when making any changes to a treatment regimen.

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 therapeutic windows, above or below which efficacy may wane. Tricyclics for which serum therapeutic levels distribute along a bell curve distribution represent one such 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).

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?

- When using two (or more) pharmacological cotherapies, is optimized dosing more useful or unnecessary for adjunctive as well as primary agents?
- For medications with established therapeutic serum levels (see Chapter 7), should dosing routinely continue toward the therapeutic range if the patient markedly improves at a subtherapeutic dosage?

Supratherapeutic dosing (defined as exceeding a manufacturer's maximum dose as approved by a regulatory agency such as the US Food and Drug Administration (FDA)) is limited pragmatically by drugs with narrow therapeutic indices (such as lithium or tricyclic antidepressants), dose-related adverse effects, or issues such as physiological tolerance or dependence. While *optimized* dosing (defined as achieving a maximally tolerated drug dose within the parameters of a drug manufacturer's label) is common practice in the setting of incomplete responses or loss of efficacy, despite continued pharmacotherapy, evidence to support greater efficacy from *supratherapeutic* dosing in those settings is largely anecdotal, as described more fully in Part II of this book.

G 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.

Tip

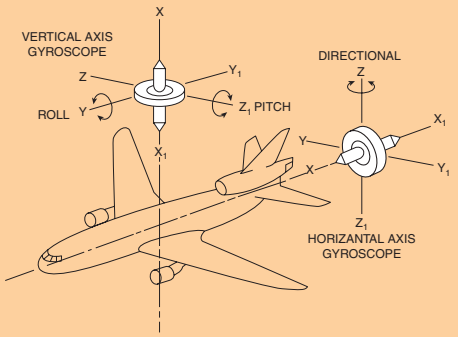
Meaningful improvement is judged not simply by a reduction in symptoms but, as importantly, by the ability to manage life stresses without incurring a resurgence or worsening of psychopathology.

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.

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 daily life stresses.



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.

H IF IT WORKED BEFORE, WILL IT WORK AGAIN?

There is more conjecture than evidence about assumptions that if a psychotropic drug was efficacious at some point in the past, it should expectably evoke the same clinical response on rechallenge after discontinuation. The trouble with questions such as this involves presuming that the clinical profile of a psychiatric problem that occurred in the remote past will re-present with the same characteristics many years later, or, ignoring the impact of new comorbidities, medical problems, concomitant drugs, or changes in hepatic or renal function over time. Nevertheless, there exists at least some data showing that in the case of chronic depression, retreatment with a tricyclic antidepressant after initial response again yielded robust benefit in slightly over 90% of patients (Friedman et al., 1995). In bipolar disorder, some authors have reported cases of lithium discontinuation-induced refractoriness, particularly when cessation is abrupt (over less than two weeks), while others have challenged such observations as being purely anecdotal. A 2013 meta-analysis of five studies involving 212 patients found no statistically significant reduction in lithium's prophylactic efficacy upon reinstitution after discontinuation (de Vries et al., 2013).

Our perception of such reports, particularly in the absence of adequately powered trials designed and devoted to assess true loss of efficacy or tachyphylaxis, is that because many real-world factors confound treatment stops and starts, it is difficult to form reliable generalizations about lesser efficacy upon psychotropic rechallenges. To the extent that clinical circumstances bear sufficient resemblance from one presentation to another in the same patient, a known history of favorable previous response to a given medication likely bodes well for its future success upon reinitiation.

I DO MECHANISMS OF ACTION MATTER?

All psychotropic drugs, from lithium to SSRIs to antipsychotics to psychostimulants to sedative-hypnotics, carry language in their manufacturers' product labels (usually found in Section 12.1) to the effect that the exact mode of therapeutic action for treating [the clinical condition of interest] is not known (or "unclear" or "not fully understood," depending on wording for a given agent). Is this simply a medicolegal disclaimer? Not entirely. While animal or other preclinical studies provide some knowledge about brain structures and neurotransmitter systems affected by a given drug, a considerable inferential leap is often needed to extrapolate those findings to observed human pharmacodynamic effects. Broad pharmacodynamic conclusions based solely on a mechanism of action also run the risk of implying class effects where none may exist. For example, not all GABAergic anticonvulsant drugs have mood-stabilizing, or anxiolytic, or antinocioceptive properties – some do, some do not, and seldom is one drug "within class" interchangeable for another.

Neurotransmitter pathways also may exert different effects in different brain regions (for example, dopamine agonism may promote attentional processing in the prefrontal cortex but have psychotomimetic effects in mesolimbic pathways). Finally, modern thinking about neural circuits points more to broad architectural pathways of circuits that interact with one another across brain regions, rather than "single" regions as a solitary focus of brain function or pharmacodynamic activity.

Some psychotropically active compounds have extremely diverse mechanisms of action (MOAs). In such instances, especially when the putative MOA to explain a particular psychotropic effect could be one of many, it becomes impractical if not senseless to try to formulate a classifiable descriptor based on receptor or enzymatic or neurotransmitter profiles. Consider, for example, the case of ketamine, a multipurpose drug for which its antagonism at the *N*-methyl-D-aspartate (NMDA) receptor is thought to mediate its dissociative anesthetic effects but not necessarily its antidepressant properties. (As described further in Chapter 13, a number of NMDA receptor antagonists other than ketamine have been shown to be no better than placebo for treatment of depression.) It would be mechanistically accurate, but awfully cumbersome and none too pithy to speak of ketamine as an exemplary drug that antagonizes NMDA, μ opioid, α_7 nicotinic, and M_1, M_2 and M_3 muscarinic receptors while agonizing D_2 and σ_1 or σ_2 receptors as well as inhibiting serotonin reuptake inhibitor (SERT), norepinephrine transporter (NET), dopamine transporter (DAT), and acetylcholinesterase.

For that matter, to the extent that every atypical antipsychotic also has a unique molecular signature with respect to its binding affinity and differential ratios of one neurotransmitter system to another (e.g., $5HT_{2A}$:D_2), broad mechanistic classifications may not tell enough of the story to account for relevant psychotropic effects, or even "best in