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?

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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?

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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

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(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

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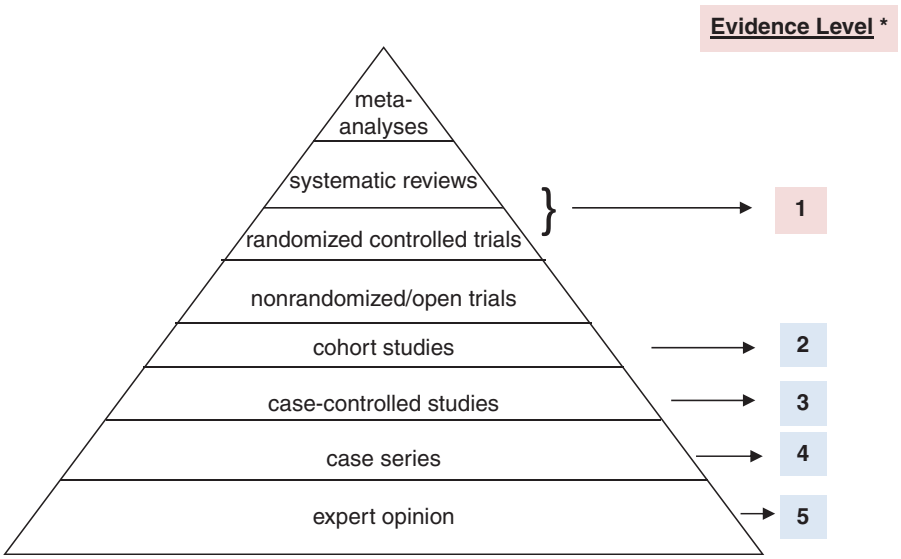
Figure 1.1 Levels of evidence in clinical trials.



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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

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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;

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- 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?

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- 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

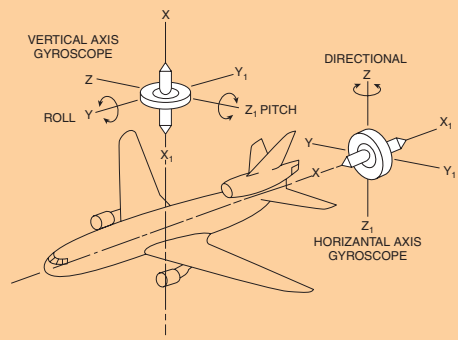
Meaningful improvement is judged not simply by a reduction in symptoms but, as importantly, by the ability to manage life stresses without incurring a resurgence or worsening of psychopathology.

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.

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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

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class" designations (e.g., clozapine versus all other atypical antipsychotics). Within a classable MOA, drugs also may vary in their central nervous system (CNS) penetration (e.g., β-blockers crossing the blood–brain barrier), potency (e.g., tramadol and ziprasidone are both serotonin-norepinephrine reuptake inhibitors (SNRIs), albeit weakly so), receptor subtype selectivity/nonselectivity (e.g., α-agonists, monoamine oxidase inhibitors (MAOIs)), or dose-related recruitment of one system over another (e.g., venlafaxine functions predominantly as an SSRI rather than an SNRI at low doses; ziprasidone at low doses (e.g., <120–160 mg/day) functions more as a $5HT_{2C}$ antagonist than a D_2 antagonist (Mattei et al., 2011)).

J NO MORE "CHEMICAL IMBALANCE" OVERSIMPLIFICATIONS

In the 1960s, the so-called catecholamine hypothesis of mood disorders held that relative overabundances or deficiencies of monoamines were responsible for externalizing states (such as mania or psychosis) or internalizing states (such as depression or negative/deficit symptoms), respectively. Such simplified concepts failed to take into account different effects of particular neurotransmission in one brain region versus another (e.g., low hypodopaminergic tone is associated with inattention and low motivation in prefrontal circuitry but parkinsonism in the striatum), or interactions between pathways that might operate through different transmitter systems (e.g., the role of gamma aminobutyric acid (GABA) interneurons that serve to "turn on" or "turn off" other circuits).

Another point of uncertainty involves generalizations about expectable pharmacodynamic effects based on a drug's MOA. Here things can become tricky. For instance, likely all D_2 antagonists have antipsychotic properties, but not all antipsychotic drugs treat depression, and some may even cause or exacerbate depression. Similarly, anticonvulsants vary considerably in their psychotropic effects. In the 1990s, many anticonvulsant drugs were presumed to exert mood-stabilizing effects based on the presence of GABAergic activity (putatively antimanic) or antiglutamatergic activity (putatively antidepressant). This theory neatly fits the biochemical relationship of glutamate and GABA in presynaptic neurons and their respective effects on neuronal excitation or inhibition, but then fails to account for numerous subsequent negative or failed trials of newer anticonvulsants (such as gabapentin, topiramate, tiagabine, and others) in studies to treat mood symptoms in bipolar disorder. The model does help to account for the relative lack of antimanic efficacy of lamotrigine (as an antiglutamatergic but non-GABAergic compound) and the only modest antidepressant impact of divalproex (as a GABAergic agent). However, as a broad concept, it failed to account for the relative absence of mood-stabilizing effects seen in a host of other GABAergic or antiglutamatergic compounds that followed.

Examples of the diversity of relationships between psychotropic agents, their known pharmacodynamic effects, and evidence regarding their putative MOAs are presented in Table 1.8 at the end of this chapter.

K ON-LABEL AND OFF-LABEL DRUG USES

Approval by drug regulatory agencies such as the FDA is not necessarily synonymous with evidence-based medicine or the scientific rationale behind using a particular drug for a unique patient. Drug manufacturers pursue regulatory agency approval for proprietary formulations or molecular compounds for which generic versions are unavailable and sufficient patent life remains active for the drug of interest, usually when there is a large enough market share to justify the enormous expenditure of time and financial resources necessary to obtain regulatory approval.

The pursuit of regulatory agency approval for a new chemical entity (NCE) is a lengthy process divided into phases, as described in Table 1.9 at the end of this chapter. It is important for both clinicians and patients to recognize that distinctions between "on-label" and "off-label" uses according to regulatory agencies such as the FDA mainly reflect the outcome of efforts by drug manufacturers with vested interests in marketing proprietary products. Generic compounds or drugs whose patent lives have expired may indeed have demonstrable efficacy and safety from Level 2- or even Level 1-evidence studies (see Figure 1.1), but without the substantial resources necessary to pursue a regulatory agency-approved indication, many evidence-based treatments remain off label. Given that 95% of drugs tested in Phase 0 and Phase I trials fail to demonstrate adequate safety and efficacy to justify their further development, and that the cost to bring a new drug to market may be as high as $5 billion, one must appreciate the economic versus scientific basis for "on-label" drug designation and marketing as wholly separate from the rigor with which evidence may exist for "off-label"

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pharmacodynamic efficacy. Examples of such evidence-based but "off-label" drug uses abound within clinical psychopharmacology and include the following:

- **Gabapentin for anxiolysis:** A positive 14-week RCT in social anxiety disorder found a 38% response rate; data are less robust in generalized anxiety disorder (GAD) (Mula et al., 2007);
- **Lamotrigine for acute bipolar depression:** Five randomized placebo-controlled trials collectively demonstrated significant greater likelihood of response with lamotrigine than placebo, specifically in patients with high baseline severity (Geddes et al., 2009);
- **Lurasidone for major depressive disorder with mixed features (MDD-MF):** No psychotropic drug carries FDA approval for this newly described DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) diagnostic entity; however, one six-week RCT showed significant reduction in both manic and depressive symptoms with large effect size, low discontinuation due to intolerance (Suppes et al., 2016);
- **Modafinil for attention deficit hyperactivity disorder (ADHD):** Five multisite RCTs showed significantly greater reduction in ADHD severity scores than placebo with medium-to-large effect size, fivefold decreased appetite, sixfold decreased insomnia, no cardiovascular adverse effects, dropouts due to adverse effects comparable to placebo (meta-analysis by Wang et al., 2017a);
- **Pregabalin for GAD:** Eight placebo-controlled trials demonstrated significant efficacy but with only a small-to-medium effect size, comparable response rates to benzodiazepines, no differences from placebo in dropout due to adverse events (Generoso et al., 2017);
- **Quetiapine for GAD:** Three placebo-controlled trials showed better response and remission rates than placebo for quetiapine XR 50 or 150 mg/day, comparable efficacy and discontinuation due to adverse effects as SSRIs (meta-analysis by Maneeton et al., 2016);
- **Quetiapine for MDD:** Three RCTs showed better response and remission rates than placebo for quetiapine XR 50 or 150 mg/day, comparable efficacy and discontinuation due to adverse effects as SSRIs (meta-analysis by Maneeton et al., 2016);
- **Topiramate for alcohol use disorder:** Seven placebo-controlled trials showed significant improvements with medium effect sizes in heavy drinking days and abstinence, smaller effect/nonsignificant for craving (meta-analysis by Blodgett et al., 2014).

WHAT'S IN A NAME?

The nomenclature by which we classify psychotropic (and many nonpsychotropic) drugs is often antiquated and increasingly uninformative with respect to the actual specific pharmacodynamic effects of a specific drug. Not all anticonvulsants treat all forms of epilepsy, not all antineoplastic drugs treat all neoplasms, and not all antidepressants treat all forms of depression. Paradigm shifts are far from new in psychiatry, and drug classification by an original indication quickly can become uninformative – MAOIs are no longer called antituberculosis drugs, chlorpromazine is no longer the preanesthetic sedative that it was in the 1950s, and many anticonvulsants are nowadays prescribed for bipolar disorder or migraine or neuropathic pain irrespective of their anticonvulsant origins. Meanwhile, some "non-antidepressants" are evidence-based for some forms of depression, to the consternation of many clinicians wedded to an old and increasingly archaic nomenclature. Consider Clinical Vignette 1.2.

CLINICAL VIGNETTE 1.2

Arthur was a 34-year-old man with bipolar I disorder being treated with lamotrigine 400 mg/day, lurasidone 40 mg/day, armodafinil 250 mg/day, and *N*-acetylcysteine 1800 mg/day. He nevertheless complained of persistent depression and his psychotherapist called his psychiatrist to ask why he was not taking an antidepressant. The psychiatrist, who was thoroughly familiar with the content of Chapter 13 of this book, needed to explain that no "traditional" antidepressant has ever demonstrated efficacy greater than that of a mood stabilizer alone, but that each of the four compounds Arthur was taking had at least one (if not more) randomized, double-blind, placebo-controlled trials to support efficacy for bipolar depression, with at least moderate effect sizes, and nonredundancy (and possible pharmacodynamic synergy) in their respective putative mechanisms of action. The therapist, nevertheless, felt the psychiatrist was still remiss in not prescribing "an antidepressant."

Table 1.10 provides examples of medications whose evidence-based psychotropic drug effects have little or no correspondence with broader "classifications" by which they are often popularly recognized. Drugs that possess multiple evidence-based pharmacodynamic effects hold special importance in the hearts and minds

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of psychopharmacologists. Like Swiss army knives that do far more than simply perform expected knife duties, or smart phone devices whose functional utility may have little or no relevance to telephone capabilities, our nomenclature is expanding to capture the varied actual psychotropic properties vis-à-vis putative mechanisms of action. Not all antituberculosis drugs treat depression (iproniazid), nor do all antihypertensives treat tremor (propranolol).

M NEUROSCIENCE-BASED NOMENCLATURE (NBN)

In 2010, the European College of Neuropsychopharmacology (ECNP) established a task force to reassess and revise the terminology with which psychotropic drugs are classified. The resulting neuroscience-based nomenclature (NbN) attempts to classify medications based on a drug's pharmacology and putative mode of action, alongside its clinical indication (see www.nbn2.com). Representative examples of this classification system are provided in Table 1.11. (Note that many drugs have multiple mechanisms of action and are thus classifiable under more than one heading.)

In some instances, uncertainty or ambiguity about a drug's mode of action leads to classifications that may not be so directly useful (e.g., the NbN identifies lithium's mode of action as "enzyme interactions"), or a putative mechanism may involve so many receptors as to defy a *general* classification (e.g., vortioxetine). Others may have such elaborate putative mechanisms of action so as to make a broad categorization based on mode of action unduly cumbersome, if not simply overspeculative. Examples here might include topiramate (whose mode of action is described as "facilitation of GABA transmission, receptor antagonist on AMPA or kainic acid"). Ketamine's MOA may vary across its diverse pharmacodynamic properties – its anesthetic effects may stem from its NMDA receptor antagonism, while its analgesic effects may relate to both its anti-NMDA receptor properties plus its μ opioid receptor blockade; its apparent antidepressant effects are presently hypothesized to come from its activation at α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors or σ_1 and σ_2 receptors more likely than from its NMDA receptor-blocking effects – making it hard to neatly "class" the drug based on numerous mechanisms of action that may pertain to different pharmacodynamic effects (e.g., analgesic versus antidepressant properties).

N DEFINING THE GOALS OF TREATMENT

All too often, patients and clinicians embark on a treatment regimen with little or no explicit discussion about realistic goals and expectations. Seldom does psychopharmacology magically transform all mental health blemishes, particularly when problems are longstanding and complex, making it important to identify specific targets of treatment, acknowledge limitations, agree on practical goals and priorities, and clarify what is and is not likely to be pharmacologically remediable. Staunch refusal to accept or tolerate annoying but medically nonhazardous adverse drug effects often means foregoing aggressive medication regimens. Histories of extreme treatment resistance (involving nonresponses to numerous adequate and appropriate medication trials) portend a low (though not necessarily nil) probability of substantial improvement, as opposed to making less substantial, more modest possible inroads for certain symptoms in managing a chronic condition. Longstanding or deeply engrained negative attitudes or beliefs, unhealthy lifestyle choices, poor adaptation or coping skills, marked distress intolerance, or dissatisfaction with life circumstances all may require interventions other than pharmacotherapy.

In palliative care medicine, the concept of "defining the goals of care" provides a useful example of establishing unambiguous expectations and clear priorities about targeted treatment outcomes. It is a reality that even with excellent pharmacotherapy, response and remission rates for many serious psychiatric conditions are far less than 100%, while relapses and recurrences are sometimes inevitable and unavoidable despite proper care. Particularly in chronic conditions that have not responded to multiple appropriate biological therapies, adopting a "disease management" rather than a "disease modification" approach often becomes an unspoken necessity.

Defining the goals of care in an explicit manner from the outset can help to temper unrealistic expectations and effectively "set the bar" low enough that *any* improvements will be more likely hailed than discounted. Examples of key targets that could serve as goals of treatment unto themselves might include:

- restoring disrupted sleep or appetite
- averting emergency department visits, hospitalizations, or suicide attempts

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- maintaining work role functioning and minimizing absenteeism/presenteeism
- maintaining an independent living status
- minimizing the cumulative burden of adverse drug effects by pruning ineffective medications

Tip

Know exactly what symptoms are the intended targets of any purposeful intervention.

- strengthening coping skills and striving to improve quality of life despite the incomplete resolution of psychiatric symptoms

In the pages ahead, we urge the reader to keep in mind the particular goals of treatment specific to each patient they encounter, rather than simply the notion of trying to ameliorate a diagnosis as if the process were generic and divorced from the patient-specific characteristics that drive treatment outcome as discussed throughout subsequent chapters.

TAKE-HOME POINTS

- Critically examine the evidence behind suspected cause-and-effect relationships when prescribing medications and judging presumptive efficacy, lack of efficacy, or adverse effects, versus the natural course of illness. Impose Hill criteria for causality.
- Recognize the degree of rigor and evidence base to support the utility of treatment interventions. Randomization is the "great equalizer" that accounts for confounding factors that can differentially influence outcome within clinical subgroups.
- While adequate pharmacotherapy trials often require many weeks to assess, just-noticeable differences often should be apparent by two weeks; their absence at this benchmark may signal the need to alter medication doses or otherwise modify a treatment plan in order to optimize eventual response or remission. By the same token, have a specific rationale in mind to justify decisions behind changes to a treatment regimen.
- When judging treatment efficacy, consider not only symptomatic improvements but also signs that a patient has an improved capacity to withstand normal daily stresses.
- Favor complementary over redundant drug mechanisms of action when combining pharmacotherapies or choosing plausible rationales behind medication decisions.
- Have clear and specific therapeutic goals in mind when making any changes to a treatment regimen.

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Table 1.1 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: cholinergic system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
ACh (subtypes: muscarinic: M_1–M_5; nicotinic)	Basal forebrain (i.e., the septal nuclei and the nucleus basalis of Meynert) projections to PFC, hippocampus, and amygdala; the laterodorsal tegmental and pediculopontine nuclei, projecting to thalamus, pons, medulla, cerebellum, and cranial nerve nuclei; and cholinergic projections from the caudate nucleus	M_1 *agonists* (e.g., xanomeline) may enhance attention, verbal reasoning, and memory while *antagonists* (e.g., benztropine, diphenhydramine, oxybutynin, tricyclics) may cause cognitive dulling. M_3 *agonists* stimulate salivary and other glandular secretions; *antagonists* (e.g., oxybutynin) may cause urinary retention. Some nicotinic *agonists* may aid cognition (e.g., galantamine), particularly those binding at the α_7 subunit, at least theoretically, or smoking cessation (e.g., varenicline); *antagonists* may also help smoking cessation (e.g., bupropion) or act as nondepolarizing neuromuscular blockers (e.g., atracurium, pancuronium).

Abbreviations: Ach = acetylcholine; PFC = prefrontal cortex

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Table 1.2 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: dopaminergic system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
D_1	Dorsal striatum (caudate, putamen), ventral striatum (NAc, olfactory tubercle), PFC and temporal cortex	*Agonism* in PFC may enhance working memory and social cognition, and in striatum may produce antiparkinsonian effects (e.g., pergolide, rotigotine); *antagonism* may produce antipsychotic effects (most FGAs and SGAs) and sometimes antidepressant effects.
D_2	*Postsynaptic* receptors found in nigrostriatal (substantia nigra pars compacta → caudate and putamen), mesocortical (ventral tegmentum → PFC), mesolimbic (ventral tegmentum → ventral striatum (NAc, olfactory tubercle)), tuberinfundibular (arcuate nucleus of the hypothalamus → pituitary) tracts. Postsynaptic D_2 receptors are also found as heteroreceptors on nondopaminergic neurons. *Presynaptic* D_2 autoreceptors are most densely concentrated in ventral tegmentum and substantia nigra pars compacta	*Agonism* at postsynaptic receptors may enhance attention (PFC) and reward (mesolimbic), diminish parkinsonian movements (nigrostriatal), and counteract hyperprolactinemia (tuberoinfundibular); *postsynaptic antagonism* produces antipsychotic and Parkinsonism effects, hyperprolactinemia; *presynaptic agonism* downregulates DA release, producing similar effects to those seen with postsynaptic antagonism
D_3 (D_2-like)	*Presynaptic*. High concentrations in ventral striatum (NAc, olfactory tubercle), thalamus, hippocampus, motor regions (e.g., putamen)	*Agonists* (e.g., bromocriptine, pramipexole, rotigotine) may enhance motivation or aggravate psychosis; *partial agonism* (e.g., aripiprazole, brexpiprazole, cariprazine) may contribute to antidepressant effects; *selective antagonism* could exert anticraving and antipsychotic efficacy (though lesser affinity than for D_2 receptors; e.g., nemonapride[a]) while potentially sparing adverse cognitive and motor effects associated with D_2 blockade
D_4 (D_2-like)	Frontal cortex, medulla, hypothalamus, striatum, NAc	May play a role in novelty-seeking, working memory, fear-based memory; clozapine potently antagonizes D_4 receptors
D_5 (D_1-like)	Found in PFC, amygdala, hippocampus, thalamus, striatum, cerebellum, basal forebrain	No selective agents available; may be associated with fear-based memory, smoking initiation

[a] Not available in the USA

Abbreviations: DA = dopamine; FGA = first-generation antipsychotic; NAc = nucleus accumbens; PFC = prefrontal cortex; SGA = second-generation antipsychotic

Note: DA concentrations are said to follow a U-shaped curve (∩) in relation to working memory; too high or too low basal DA levels seem to impair cognitive function; optimal functioning occurs in a middle-ground "Goldilocks" zone

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Table 1.3 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: serotonergic system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
$5HT_{1A}$	Presynaptic somatodendritic autoreceptors in raphe nucleus; postsynaptic receptors in limbic system, hypothalamus, cortex, dorsal horn	*Presynaptic agonism* downregulates (while *antagonism* upregulates) serotonergic release; *postsynaptic agonism* associated with antidepressant and anxiolytic effects
$5HT_{1B}$	PFC, basal ganglia, striatum, hippocampus	*Antagonism* associated with antidepressant effects
$5HT_{2A}$	PFC, parietal and somatosensory cortex, olfactory tubercle, hippocampus	*Antagonism* increases prefrontal DA release, may enhance attention and working memory; *agonism* associated with psychedelic effects of serotonergic hallucinogens (e.g., LSD), enhanced associative learning, release of oxytocin, prolactin
$5HT_3$	Cortex, hippocampus, NAc, ventral tegmentum, substantia nigra, brainstem (area postrema and nucleus tractus solitarius)	*Agonists* enhance release of DA, GABA, CCK; affects vomiting reflex, cognition, anxiety while *antagonists* (e.g., ondansetron, granisetron, zacopride, phenothiazines) produce antiemetic, anticraving, and possible antipsychotic effects
$5HT_7$	Thalamus, hypothalamus, amygdala, hippocampus, dorsal raphe, caudate, putamen, substantia nigra	*Agonism* enhances GABA-mediated inhibition of 5HT in raphe nucleus (effectively decreasing 5HT release), enhances GABAergic inhibition and increases glutamatergic stimulation in hippocampus, may influence mood, learning and memory, sleep–wake cycle, thermoregulation, nocioception

Abbreviations: CCK = cholecystokinin; DA = dopamine; GABA = gamma-aminobutyric acid; 5HT = serotonin; LSD = D-lysergic acid diethylamide; NAc = nucleus accumbens; PFC = prefrontal cortex

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Table 1.4 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: noradrenergic system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
NE	Pons (locus coeruleus)	α_1 *agonists* (e.g., phenylephrine) vasoconstrict; *antagonists* can cause orthostatic hypotension, may reduce nightmares associated with PTSD (e.g., prazosin); α_2 *agonists* (e.g., clonidine) cause sedation and blunt autonomic hyperarousal (e.g., during opiate withdrawal); α_2 *antagonists* (e.g., yohimbine) may counteract erectile dysfunction but increase blood pressure and cause anxiety; β_1 *agonists* (e.g., dobutamine) increase heart rate and cardiac contractility (e.g., to treat congestive heart failure); *antagonists*[a] are cardioselective to treat hypertension and tachycardia; β_2 *agonists* (e.g., albuterol) bronchodilate, delay premature labor (e.g., terbutaline); *antagonists* lack known clinical use

[a] Nonselective β1 and β2 antagonist examples include propranolol, pindolol, nadolol, labetolol, carvedilol

Abbreviations: NE = norepinephrine; PTSD = post-traumatic stress disorder

Table 1.5 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: GABA/glutamate system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
GABA	The major inhibitory neurotransmitter, distributed widely throughout cortical and subcortical (e.g., basal ganglia) brain regions	GABA *agonism* can produce sedative, anxiolytic, and anticonvulsant effects. GABA interneurons often function as "feed forward" or "feed backward" circuit-breakers (meaning, they function like on/off switches) by inhibiting other circuits within a neural network
Glu	Cortico-brainstem, corticostriatal (PFC → striatum and NAc), thalamo-cortical, cortico-thalamic, corticocortical (intra-cortical pyramidal neurons) pathways	Regional binding may influence attention, learning and memory, psychosis, pain perception, parkinsonism

Abbreviations: NAc = nucleus accumbens; PFC = prefrontal cortex

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Table 1.6 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: histamine system

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
H_1	Highest densities in frontal, temporal and occipital cortices, cingulate gyrus, striatum, thalamus	*Antagonism* associated with sedation, cognitive dulling, weight gain, relief from allergic reactions
H_2	Distributed throughout cortex, caudate, putamen, hippocampus	*Antagonism* may impair memory and cognition
H_3	Prominent in basal ganglia, globus pallidus, hippocampus, cortex	Presynaptic inhibitory heteroreceptor. *Antagonism* may broadly affect cognition via enhancing release of histamine, ACh, NE, DA, among other neurotransmitter systems. Pitolisant, a novel H_3 receptor antagonist/inverse agonist received FDA approval as a nonscheduled pharmacotherapy for narcolepsy in 2019

Abbreviations: ACh = acetylcholine; DA = dopamine; NE = norepinephrine

Table 1.7 Brain distribution of neurotransmitter targets and their pharmacodynamic effects: melatonin and orexin systems

Neurotransmitter targets	Regional locations	Putative pharmacodynamic effects
Melatonin	Pineal gland	*Agonists* (e.g., ramelteon) may promote sleep by synchronizing circadian rhythms
Orexin	Perifornical area and lateral hypothalamus	*Antagonists* of orexin A (ORA) and orexin B (ORB) receptors (e.g., suvorexant) may promote sleep by downregulating activity of the ascending arousal pathway and upregulating sleep-promoting brain nuclei (notably, the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus)

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Table 1.8 Diverse relationships between psychotropic drug effects and presumed mechanisms of action

Agent	Clinical disorders of interest	Proposed mechanism(s) of action	Conflicting evidence
Amphetamine	ADD/ADHD, depression	↑ extracellular DA via: (a) decreasing presynaptic DA uptake by competitively inhibiting uptake at the DA transporter, (b) facilitating DA vesicle release into the cytoplasm through VMAT2 binding, and (c) increasing intrasynaptic DA and NE by reversing the direction of transport through DA and NE transport proteins into the synaptic cleft	None
Anticonvulsants	Bipolar disorder, epilepsy, anxiety disorders	GABAergic and antiglutamatergic effects	Most anticonvulsants apart from divalproex, carbamazepine and lamotrigine show no benefit for mood disorders
Ketamine	Depression; depression with suicidal ideation	NMDA receptor antagonism; sigma receptor blockade; μ opioid receptor blockade	Other antiglutamatergic drugs (such as riluzole, memantine and lanicemine) have not demonstrated antidepressant efficacy
Lithium	Bipolar disorder, impulsivity, suicide	Numerous proposed mechanisms involving intracellular second messenger and signal transduction pathways, as well as neurotrophic and anti-apoptotic effects	Not all proposed mechanisms broadly affect mood (e.g., some but not all PKC inhibitors (see Chapter 13))
SNRIs	Depression, anxiety, pain	Increased presynaptic 5HT and NE availability via reuptake inhibition	None
SSRIs	Depression, anxiety	Increased presynaptic 5HT availability via reuptake inhibition	None
DORAs	Insomnia	Suvorexant, lemborexant are dual orexin receptor antagonists	None

Abbreviations: 5HT = serotonin; ADD = attention deficit disorder; ADHD = attention deficit hyperactivity disorder; DA = dopamine; DORA = dual orexin receptor antagonist; GABA = gamma aminobutyric acid; NE = norepinephrine; NMDA = *N*-methyl-D-aspartate; PKC = protein kinase C; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VMAT2 = vesicular monoamine transporter 2

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Table 1.9 Phases of drug development

Preclinical	Phase 0	Phase I	Phase II	Phase III	Phase IV
Animal or in vitro studies conducted to identify pharmacokinetic properties (dosing, metabolism) and determine if a proposed drug is safe for human exposure	Microdosing in a small number of healthy human subjects to obtain further information about pharmacokinetics (e.g., bio-availability, half-life) and drug safety	Somewhat larger trials in healthy human subjects to clarify dosing and safety	Larger trials on a patient population to gauge likely efficacy and adverse effects	Large-scale trials in patient populations to provide a more definitive assessment of drug efficacy and safety	The collection of post-marketing surveillance (also called pharmaco-vigilance) data to gauge long-term effects during routine treatment
			Phase IIa: Pilot trials in selected populations; **Phase IIb**: Rigorous, well-controlled, "pivotal" trials	**Phase IIIa**: Additional safety and efficacy data after initial efficacy has been demonstrated, prior to regulatory submission; **Phase IIIb**: conducted after regulatory submission but prior to approval and launch	

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Table 1.10 Distinctions between common drug "classifications" and their evidence-based uses

Classification	Examples	Evidence-based uses unrelated to classification
Anticonvulsants	Carbamazepine	Bipolar disorder; trigeminal neuralgia
	Gabapentin	Neuropathic pain; anxiety; insomnia
	Lamotrigine	Bipolar disorder
	Topiramate	Migraine; weight loss; alcoholism
Antidepressants	Bupropion	Smoking cessation; weight loss
	Duloxetine	Stress incontinence; chronic low back pain
	Nortriptyline	Migraine, neuropathic pain
Antihistamines	Diphenhydramine	Insomnia
	Hydroxyzine	Anxiety
	Trimethobenzamide	Nausea
Antihypertensives	Propranolol	Tremor; performance anxiety; migraine
	Clonidine	ADHD; opiate withdrawal; tics
	Guanfacine	ADHD; tics
Antipsychotics	Aripiprazole	Major depression; bipolar mania
	Brexpiprazole	Major depression; bipolar mania
	Cariprazine	Bipolar mania; bipolar depression
	Lurasidone	Bipolar depression
	Quetiapine	Depression; bipolar mania/depression; anxiety

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Table 1.11 Examples of neuroscience-based nomenclature[a]

Putative mechanism	Examples
ACh inhibitor	Donepezil
DA reuptake inhibitor	Modafinil
DA/NE reuptake inhibitor/ releaser	Amphetamine, lisdexamfetamine, methylphenidate
Enzyme inducer	Lithium carbonate (inositol monophosphatase, protein kinase C, glycogen synthase kinase-3)
Enzyme inhibitor	Selegiline (MAO-A, MAO-B)
Irreversible enzyme inhibitor	Isocarboxazid, phenelzine (MAO-A, MAO-B)
Partial agonist	Buprenorphine (μ); buspirone, cariprazine, vilazodone ($5HT_{1A}$); varenicline ($\alpha_4\beta_2$ and $\alpha_6\beta_2$)
Positive allosteric modulator	Acamprosate, alprazolam, clonazepam ($GABA_A$)
Receptor agonist	Clonidine, guanfacine (α_1); melatonin, ramelteon (M_1, M_2); prazosin (α_1); varenicline (α_7 nicotinic)
Receptor antagonist	Buprenorphine (κ, δ); olanzapine, ziprasidone (D_2, $5HT_{2A}$); clozapine, paliperidone, risperidone (D_2, $5HT_{2A}$, α_1); flumazenil ($GABA_A$); diphenhydramine, hydroxyzine (H_1); ketamine, memantine (NMDA); prazosin, quetiapine, risperidone, trazodone (α_1); mirtazapine[†] ($NE\alpha_2$, $5HT_{2A}$, $5HT_3$); nefazodone, pimavanserin, trazodone ($5HT_{2A}$); vortioxetine ($5HT_{1D}$, $5HT_3$, $5HT_7$)
Receptor partial agonist/ receptor antagonist	Aripirazole, brexpiprazole, cariprazine (D_2, $5HT_{1A}$/$5HT_{2A}$)
Reuptake inhibitor	Atomoxetine, desipramine, maprotiline, nortriptyline, reboxetine (NET); bupropion (NET, DAT); fluoxetine, sertraline, vilazodone, vortioxetine (SERT); clomipramine, duloxetine, imipramine, levomilnacipran, venlafaxine, desvenlafaxine (SERT, NET); suvorexant (OR1, OR2)
Voltage-gated Ca^{++} channel blocker	Carbamazepine, gabapentin, oxcarbazepine, pregabalin
Voltage-gated Na^{+} channel blocker	Acamprosate, divalproex

[a] As modified from www.nbn.com

[†] Mirtazapine is sometimes referred to as a noradrenergic and specific serotonergic antidepressant (NaSSA)

Abbreviations: 5HT = serotonin; DA = dopamine; DAT = dopamine transporter; GABA = gamma aminobutyric acid; MAO = monoamine oxidase; NE = norepinephrine; NET = norepinephrine transporter; NMDA = *N*-methyl-D-aspartate; OR = orexin; SERT = serotonin reuptake transporter

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