

Chapter 9. Effects of Drugs

Major Points

- **There already exist the six categories of FDA approved drugs to strengthen or weaken each of the Big Three, and thereby perform The Adjustment.**
- **The proposed nore weakening drugs are not yet widely used by psychiatrists and their use could result in landmark improvements in treatment.**
- **The brain mechanism of the hallucinogenic street drug LSD is relevant to understanding psychotic brain states, such as those found in schizophrenia.**

The existing drugs should allow us to perform The Adjustment, and thereby for better or worse, allow us in part to undo what genetics and stress have done. Drugs may eventually, and to some extent probably already do, allow us to ‘access’ the Big Three circuitry at different points in each pathway, affecting personality traits as well as affecting mental illness characteristics. A given Big Three drug may treat more than one type of mental illness, just as it may affect many personality traits.

While we may not know the possibly harmful long-term effects of taking psychiatric drugs, we also don’t know the possibly harmful effects of having abnormal Big Three systems or mental illnesses themselves, such as potential brain damage. As mentioned in Chapter 7, there’s already a known association between depression exacerbating heart disease, and Big Three abnormalities may also be associated with other diseases.

Drugs that act on the ser and nore systems are not physically addictive in the conventional sense because they do not produce physical craving. On the other hand, such drugs can produce withdrawal effects, though these tend to be quite mild. Drugs that act directly on the dop system, such as cocaine and crystal methamphetamine, are physically addictive, and part of their addictiveness may derive from their ability to produce an immediate ‘high’. The dop D2 receptor is thought to be the principal brain receptor acted upon either directly (via boosting the level of dop), as in cocaine and crystal meth, or indirectly as in alcohol or even food itself, which is relevant to eating disorders. The reason the D2 receptor is implicated in these disorders is because it plays an important role in the brain’s normal reward system, in that stimulation of this receptor makes the person temporarily feel good.

Most psychiatric drugs with known mechanisms of action affect the Big Three, and many of the drugs with unknown mechanisms may also do so indirectly, or at least act on the same circuits. Ideally we would use ser, nore, or dop specific drugs for The Adjustment, and ideally these drugs would have no or minimal metabolic interaction, which means that one drug would not interfere with the rate at which the body breaks down and eliminates another drug. At the one extreme there are receptor subtype specific drugs (or even potentially more specific intracellular drugs), whereas at the other extreme are drugs that strengthen or weaken—or activate or deactivate multiple receptors of—more than one Big Three neurotransmitter system. The latter type of drugs casts a broader

net, though simultaneously using several drugs of the former type would be more precise for implementing The Adjustment in a given person.

A premise of the current theory is that there is no difference between altering the strengths of the Big Three with a drug and altering the strengths based on the natural functioning of the brain, which is mainly produced by genetics and also by environmental inputs such as stressors. For example, is antidepressant induced mania somehow different than mania that occurs naturally? Or is antidepressant induced wellness somehow different than normal, natural mood? The assumption here is that the drugs can produce the same effects as natural Big Three strengths.

Reversibility of effect, namely that the effects of a given drug will go away once it is discontinued—though there still are potential withdrawal effects—is an important consideration in using psychiatric drugs. This usually applies to all currently used drugs except the typical antipsychotics, which can cause tardive dyskinesia, a potentially irreversible movement disorder. Very rare irreversible effects may take place with other drugs as well, such as lithium damaging the kidneys. Another type of reversible effect is side effects that go away after taking a drug for some time. On the other hand, ECT and antidepressants may sometimes produce irreversible positive effects, such as stopping major depression. So an individual doesn't always return to the prior, baseline unmedicated state after the drugs are withdrawn.

Flux is a term I use for temporary mild depression that a person can experience while the Big Three are being adjusted with drugs. Such drug adjustments can make a person transiently worse before eventually making them better. Rapidly (daily, weekly, or even monthly) changing types of drugs and/or their dosages may produce a continuous state of flux, as in My Case Study.

Due to postsynaptic saturation discussed in Chapter 4, drugs that *strengthen* ser and/or nore shouldn't immediately have a perceptible effect, though dop drugs do. Therefore, in the treatment of mental illness, the time of day in taking ser/nore drugs should be irrelevant, except for possible side effects (unless, for some reason, the postsynaptic receptors are not saturated). In contrast, Big Three *weakening* drugs should have an immediately perceptible effect, if, in the case of ser and nore, the level of weakening exceeds the safety factor. In practice, though, most drugs that weaken ser and/or nore still take two weeks to kick in because of the safety factor. However, it has already been demonstrated that propranolol, a nore weakening drug, *immediately* affects recognition of sad facial expressions.

The current psychiatric drugs, except for perhaps the SRIs, aren't exactly 'recreational drugs' due to significant potential side effects, including withdrawal effects. And even the SRIs can have serious side effects. There may be at least three types of side effects for a Big Three drug that is intended to be transmitter specific: 1) binding to non-Big Three receptors, 2) producing a physiologically abnormal response within the targeted transmitter system (example: SRIs causing agitation), 3) producing a physiologically normal response within the targeted transmitter system that is unwanted (example: SRIs causing anorgasmia). For 3), the sexual side effects of ser strengthening antidepressants, such as Prozac, may actually be direct consequences of strengthening ser.

The brain doesn't seem to adapt or return to baseline in response to changes in Big Three strengths caused by continuously taken drug dosages, but in the rest of the

body, like the gut or the heart, there may be adaptation. For example, the SRIs often upset the gut for a few weeks while they are kicking in, but then the gut adapts and returns to normal. Maybe people who claim to have *brain* adaptation during the treatment of mental illness are softly bipolar, have a recurrent or periodic illness such as unipolar depression, or have a seasonal pattern to their illness. If there really is brain adaptation in some cases, how common is it? Does it just occur in certain subpopulations of patients or with certain drugs? Can it be ‘fooled’ by introducing a different drug from the same class, a drug from another class, or the same drug at a later time?

Within a class of drugs (say SRIs), when there’s non-response to one drug and response to another in a given person, this probably implies lack of binding to the particular receptor or receptors for the non-responding drug. (Another possibility is that the drug wasn’t absorbed properly.) In other words, when a level boosting antidepressant, or any other Big Three receptor-based drug, doesn’t work, it is usually because the key doesn’t fit the lock on a molecular scale, in terms of the drug/receptor interaction. However, just because a drug binds to a receptor doesn’t mean it will produce the intended effect. So the first place to look for variability in the effects of specific receptor-based drugs among different people is in the actual binding to those receptors. One future improvement for psychiatry would be understanding the three-dimensional structures of different alleles (variants of a gene) of the receptors and thereby figuring out how well the drugs bind, or at least seeing how alleles correlate with different Big Three traits and mental illnesses, as well as whether certain alleles predict response to certain Big Three drugs. Finally, from a pharmacological perspective, why does everyone seem to respond to street drugs, such as cocaine, LSD, and marijuana and not to antidepressants and other psychiatric drugs?

Drugs that bind directly to specific postsynaptic receptors are in principle more specific in their effects than drugs that simply raise or lower the level of the transmitter, since changing the level can affect a wide array of receptors. Drugs that directly enter the postsynaptic neurons in order to achieve their effects—which I call intracellular drugs—may also activate the brain circuitry in a very specific manner. Creating more drugs with more specific effects may lead to improved treatment of mental illness.

Scientists are already able to measure Big Three levels in the blood, urine, and cerebrospinal fluid (CSF). Measuring Big Three responses to a transmitter level altering drug such as an antidepressant, coupled with blood measurement of the drug level itself, may provide useful information about a person’s response to the drug. And to best implement The Adjustment, one could first perform baseline blood measurement of the levels of the Big Three, which would tell one which type of drug to use if indeed blood measures correlate with brain strengths.

There’s already a large body of evidence showing that antidepressants do a lot more than just affect mood. The greatest amount of evidence exists for SRIs, affecting traits related to dominance, for example. Antidepressants also seem to affect the rate and subject matter of thought in everyone, not just bipolar or depressed persons.

Are some antidepressants more effective than others at treating depression? Conventional wisdom is that every existing antidepressant provides at least some relief to about 60-80% of depressed people, but perhaps there are real differences in efficacy between drugs.

Double blind, placebo (i.e., a pill without any active drug, where the patient does not know if the pill contains the drug or not) controlled drug studies are scientific studies designed to test the efficacy of pharmaceutical drugs. In these studies, the doctor administering the drug treatment doesn't know if a given patient is receiving the active drug or a placebo, and neither does the patient, thereby eliminating psychological biases in both parties. Most such drug studies of mental illness report the fraction of people who get better versus everyone else, but what about the fraction who get *worse* when given a certain drug? This is not to be confused with those who would get worse without any drug or with a placebo. The current theory predicts that Big Three drugs should in some cases make people worse, and it would be informative to understand in which instances this occurs.

A ser or nore strength adjustment with drugs may prevent relapse to overt mental illness by keeping ser or nore reset, thereby correcting brain circuitry dysfunction while simultaneously affecting Big Three traits, such as those listed in Chapter 7—so there may be these two effects.

Now let's return to the subject of The Adjustment, which is how I believe Big Three drugs should be used to improve quality of life. There already exist the six categories of FDA approved drugs to strengthen or weaken each of the Big Three, and thereby perform The Adjustment; we'll now discuss these drugs in greater detail.

Ser Strengtheners

The standard ser strengthening drugs are the SRIs (ser reuptake inhibitors): Prozac, Zoloft, Paxil, Lexapro, and Luvox. Each of these drugs is FDA approved in the United States. These are ser level boosting drugs, and they have been used successfully to treat a wide variety of overt mental illnesses, as noted by Michael Norden in *Beyond Prozac*. Though the SRIs cause general brain—and maybe throughout the rest of the body as well—boosting of ser, the ser subtype 2A (5HT_2A) receptor may be the principal receptor that affects mental health, as My Case Study use of Zyprexa would suggest. Perhaps in the future, 5HT_2A receptor specific activators will replace the SRIs if they produce fewer side effects, such as agitation. Some people report that SRIs deaden their emotions, that they become more indifferent and less passionate while taking them. Perhaps in such cases, ser strengthening is not the appropriate adjustment.

Ser Weakeners

Ser weakening is most well established for the atypical antipsychotic drugs (which deactivate the ser 5HT_2A receptor and also deactivate dop receptors), tianeptine (a ser reuptake *enhancer* available in Europe), and cyproheptadine. The typical antipsychotic drugs, which may also weaken ser, are not as widely used now because they can cause tardive dyskinesia, a potentially irreversible movement disorder. Ser weakening is less well established for four other drugs—nefazodone, trazodone, mianserin, and ketanserin—which all deactivate the 5HT_2A receptor, but also weakly inhibit ser and/or nore reuptake, which could boost their levels and result in net ser and/or nore *strengthening*.

FDA approved atypical antipsychotics include: Clozaril, Zyprexa, Geodon, Risperdal, Seroquel, and Abilify, though the latter drug may not weaken ser. Clozaril,

which is also known as clozapine, can cause a dangerous blood disorder and is not widely used. All of these drugs can cause weight gain, which may possibly be associated with Type 2 diabetes, and Geodon can affect the heart. Therefore, these are not perceived as rather benign ‘recreational drugs’ like the SRIs, since their side effects are more often severe. That said, these have been miracle drugs for many people with bipolar disorder and schizophrenia, and Zyprexa (along with desipramine) saved my life. These drugs may also function as antidepressants, and so they should according to The Adjustment.

Tianeptine, which is currently available in Europe and not in the United States, is a ser reuptake enhancer—thereby a weakener of ser, through reduction of its synaptic level—that has been used as an antidepressant. It could be the first drug in a new class of antidepressants that may be better tolerated than SRIs. According to my theory, tianeptine should enhance the senses and emotions in some people (particularly those who have strong ser), and these may be perceived as pleasant effects. Tianeptine may treat depression by resetting ser pathways, creating an upstream ser level change that the rest of the postsynaptic circuitry adjusts to, ‘thinking’ it’s a new genetic level. In other words, as mentioned in Chapter 4, changing the Big Three strengths—either strengthening or weakening them—may serve to reset dysfunctional pathways to a new, healthy state. So it’s not just strengthening of the Big Three that can treat depression, and this is consistent with The Adjustment. If two-thirds of depressives respond to tianeptine and two-thirds of depressives respond to a given SRI, then this implies that at least some people will respond similarly to both types of drugs, consistent with the resetting hypothesis.

Cyproheptadine, a ser 5HT_{2A} receptor deactivator, is another potential ser weakening drug. It is FDA approved in the United States as an antihistamine, as it also deactivates histamine receptors. Preliminary evidence suggests that it may be useful in treating depression and schizophrenia.

Nore Strengtheners

The standard nore strengthening drugs are the tricyclic antidepressant NRIs (nore reuptake inhibitors): desipramine, nortriptyline, and protriptyline. Other tricyclic antidepressants may also be NRIs, but this is unclear due to their potential additional ser boosting. A newer NRI is Strattera, which is FDA approved for treating ADHD. Another NRI, reboxetine, is available in Europe and may eventually be available in the United States. Common side effects of the tricyclics include sedation and effects on the heart, though the effects on the heart are typically not dangerous, especially in adults. Recall from My Case Study that desipramine’s lone but significant side effect for me is heart arrhythmia. Because of these side effects, the nore strengthening drugs are not as popular as the SRIs for treating depression, though I believe they are underused and critical for implementing The Adjustment in some people. Maybe in the future, nore postsynaptic receptor subtype specific activators will replace the NRIs if the former drugs produce fewer side effects than the latter.

Nore Weakeners

The drugs that I propose to be nore weakeners—the alpha 2 adrenergic agonists, the alpha blockers, and the beta blockers—have not been used widely, if at all, to treat mental illness. All three types of drugs are FDA approved for heart related effects, such

as lowering blood pressure and stabilizing heart rate. The alpha 2 agonists may be the most important nore weakening drugs currently available for The Adjustment because they lower the brain level of extracellular nore—this has been shown in the rodent brain for one of these drugs, clonidine—whereas the alpha and beta blockers, if they enter the brain, may have more specific, limited effects on weakening nore that may or may not be useful for treating mental illness. In a number of preliminary studies, clonidine has been used successfully to terminate bipolar mania, though this drug has not come into widespread use for treating bipolar disorder. There's evidence that alpha 2 agonists lower the brain level of extracellular nore by binding to presynaptic nore autoreceptors in the brainstem. However, alpha 2 receptors may be present postsynaptically as well as presynaptically and if so, the alpha 2 agonists may, in some cases, strengthen nore instead of weaken it. Another possible shortcoming of these drugs is that they may only weaken nore temporarily, instead of weakening it in the long term. On the other hand, these drugs have been used to successfully treat opioid withdrawal in heroin addicts, consistent with brain nore weakening that lasts at least a few weeks, and I believe they indeed weaken nore on a long-term basis.

FDA approved alpha 2 adrenergic agonists include: clonidine, guanfacine, guanabenz acetate, and tizanidine; approved in the United Kingdom and pending United States FDA approval is lofexidine. There is a wide array of FDA approved alpha and beta blockers, including the beta blocker propranolol. In the future, perhaps nore reuptake enhancers, analogous to the ser reuptake enhancer tianeptine, can be synthesized, which will weaken nore. Furthermore, analogous to Zyprexa deactivating the ser 5HT_{2A} receptor and thereby weakening ser, perhaps nore weakening drugs may only need to deactivate a particular subtype of postsynaptic nore receptors—as may already be the case with certain alpha and beta blockers—to achieve their psychiatric nore weakening effect.

Finally, recall that a study of the nore weakening beta blocker propranolol indicates that nore plays a role in recognizing facial expressions of sadness. This indicates that beta blockers—and perhaps ser weakening atypical antipsychotics, tianeptine, and cyproheptadine—can exert immediate effects on the brain that could be studied in psychological experiments. Propranolol has also been used to treat migraine headaches (and so have the alpha 2 adrenergic agonists), which is consistent with beta blockers crossing the blood-brain barrier and binding to nore receptors in the brain. Preliminary evidence also indicates that propranolol can terminate bipolar mania.

Dop Strengtheners

The standard dop strengthener is the FDA approved ADHD drug, Ritalin. Two other drugs—amphetamine and cocaine—the latter of which I don't recommend using, also strengthen dop. I think the antidepressant Wellbutrin (aka Zyban) is a dop specific strengthener, though it may also strengthen nore. If Wellbutrin does strengthen nore, it would probably trigger mania in bipolar persons like ser or nore strengthening antidepressants do, but it generally does not trigger mania. And like all dop strengtheners, Wellbutrin's effects should kick in immediately—due to lack of dop saturation, and unlike the two week delay of ser and nore strengtheners—making it a unique antidepressant. However, I don't believe Wellbutrin can treat severe depression, which probably involves ser and/or nore dysfunction, but rather can provide relief to the

depressed until a proper ser and/or nore drug is found, or the depression ends spontaneously. In addition, recall that The Triangle (see Chapter 5) indicates that drugs that strengthen or weaken ser and/or nore affect dop likewise.

Dop Weakeners

The standard dop weakening drugs are the atypical and typical antipsychotics (see **Ser Weakeners**), where both types of drugs may directly weaken both ser and dop by deactivating some of their receptors. Evidence that these drugs weaken dop comes not only from pharmacological animal studies but also from their efficacy in terminating bipolar mania, both in the short term and long term. Recall from My Case Study that Zyprexa, an atypical antipsychotic, terminates or at least diminishes hypomania in me. Atypical antipsychotics are now commonly used in the long-term treatment of bipolar disorder, though typical antipsychotics, such as Haldol and Thorazine, tend to only be used to terminate bipolar mania in the short term since long-term use of these drugs can cause the movement disorder tardive dyskinesia. Since there may not be a dop safety factor in place within our brain chemistry, the effect of dop weakening from antipsychotics should take place immediately.

Mixed Drugs

Tricyclic Antidepressants

The tricyclic antidepressants are a large class of drugs that have been around for over 40 years. Some of the tricyclics, in their native form, strengthen ser as well as nore through level boosting reuptake inhibition, though in the body they may only strengthen nore due to rapid breakdown into exclusively nore strengthening molecules. For example, the tricyclics amitriptyline and imipramine are rapidly metabolized in the body into nortriptyline and desipramine, respectively, which are actually NRIs. Whether all tricyclics really are nore specific is a critical question for psychopharmacology since they are a vast and potent array of drugs. If some of the tricyclics are more ser specific even when metabolized in the body, then they represent an important alternative to SRIs, maybe with more favorable side effects.

One clue as to the mechanism of a particular psychiatric drug is whether it deadens or enhances the senses, since changing the ratio of ser to nore affects sensory perception, as described in Chapter 7. For example, this would give information regarding whether all the tricyclics strengthen nore, or at least do this more so than strengthen ser. This could be tested in psychological experiments by examining how sharp or dull one's sensory perception becomes after taking these drugs, and a similar test could be applied to any putative Big Three drug, such as Wellbutrin or the monoamine oxidase inhibitors (MAOIs), where the latter drugs are a class of antidepressants that may strengthen both ser and nore.

It should also be noted that a drug that is designed to strengthen both ser and nore—such as the relatively new antidepressants Cymbalta and Effexor, and possibly some of the tricyclics—may actually only strengthen *one* in a particular person: 1) due to drug/receptor binding variability among different people, and 2) if ser and nore weaken

each other strongly, as in The Triangle (see Chapter 5), then the transmitter that was boosted more strongly in a particular person would weaken the other transmitter.

Atypical Antipsychotics and Schizophrenia

Schizophrenia may actually be caused by weak or dysfunctional ser, rather than the widely believed strong dop hypothesis (discussed more in the next chapter). The atypical antipsychotics currently used to treat schizophrenia weaken both ser and dop directly. However, the direct weakening of dop may inadvertently strengthen ser according to The Triangle, and these direct and indirect effects on ser may compete with one another in a given person, and the winning effect may differ from person to person. Therefore, if schizophrenia is caused by weak ser, then the atypical antipsychotics may either improve it by strengthening ser, or make it worse by weakening ser further. If schizophrenia, however, is caused by dysfunctional ser, *any* ser strength change—either weakening or strengthening—would reset ser and thereby treat it. This may also produce the known antidepressant effect of the atypical antipsychotics. In other words, if the atypical antipsychotics make schizophrenia worse in some people, then schizophrenia may be caused by weak ser instead of dysfunctional ser. On the other hand, if ser resetting treats schizophrenia, then the SRIs can treat this illness, and so can tianeptine and cyproheptadine, which would be a landmark discovery.

Intracellular Drugs

An intracellular drug has to enter neurons as well as enter the brain to produce its therapeutic effect. The side effects of such a drug may be more favorable, and the effects more specific, than those of an external receptor binding drug. The standard treatments for bipolar disorder, namely lithium and the anticonvulsants (such as Depakote and Tegretol), appear to be intracellular drugs in that they may enter neurons and have effects on intracellular signaling cascades, rather than binding to external Big Three receptors. Because of the success of these drugs in terminating mania—where I think mania is predominantly caused by strong nore—I initially thought that they deactivate external nore receptors, but if this were the case, pharmacologists would have easily figured this out. Moreover, if lithium deactivates external nore receptors in the brain, it should have immediate psychological effects (other than sedation) like propranolol (a nore weakening beta blocker) does, but as far as I know this has never been demonstrated.

Even if lithium acts on intracellular signaling pathways, there's some evidence that its therapeutic effect may still be weakening of nore. (Of course, a drug that is intracellular may still act upon Big Three circuit strengths.) Indeed, like antidepressants, the effects of lithium and the anticonvulsants take at least a week to kick in, consistent with these drugs having an effect on ser/nore circuits. If they weaken nore, they should terminate NRI induced mania but probably not SRI induced mania, and likewise affect Big Three traits (see Chapter 7). It is also known that lithium can affect cognition, and possibly the anticonvulsants do so as well. This may be caused, via The Triangle, by indirectly weakening dop by directly weakening nore with these drugs, since dop affects the rate and subject matter of thought, as described in Chapter 7.

LSD

The mechanism of the hallucinogenic street drug LSD has implications not only for our understanding of schizophrenia and other psychotic brain states, but also for the current theory of ser saturation that was mentioned in Chapter 4. LSD is widely considered to be an activator of postsynaptic ser receptors, probably the 5HT_{2A} receptor, and thereby may strengthen ser and for that reason cause psychosis. However, LSD may be a weaker activator than ser itself for the 5HT_{2A} receptor, thereby competing with saturated ser for binding to the receptor and thereby weakening ser transmission and causing psychosis. If LSD really does activate postsynaptic ser receptors in a manner that strengthens ser, then ser (and nore) may not really be saturated systems, due to the drug's immediate effects. One test of the theory of LSD either being a weak activator or a deactivator of the 5HT_{2A} receptor is that a newly synthesized drug that is a known potent *deactivator* of this receptor should produce similar hallucinogenic effects.