One Pill Makes You Larger, And One Pill Makes You

BY SHARON BEGLELY 2/6/94 AT 7:00 PM

... THAT WAS 1960S PHARMACOLOGY. IN THAT turned-on, tuned-out decade, the
pharmacopeia of mind-altering drugs was about as subtle as a sledgehammer-uppers replaced
sleep, downers offered calm, hallucinogens projected visions of marmalade skies into the brain.
Many of them were illegal, and all of them threatened to stop the heart, blow out neurons or
cause permanent addiction. This is 1990s pharmacology: suffering stage fright before delivering
a speech? Pop a little orange pill. Moping around in the winter doldrums? Try a white one.
Want to boost your self-esteem, focus better on your work, tame the impulse to shop till you
drop, shrug off your spouse's habit of littering the floor with underwear, overcome your shyness
or keep yourself from blurt out your deepest secrets to the first stranger who comes along?
Science has, or soon will have, just the legal, doctor-prescribed pill for you.

It's gone beyond Prozac. That antidepressant has spawned a culture of pill poppers: people who
do not suffer from severe depression (for which the Food and Drug Administration approved
Prozac in 1987) but who find that the little green and white capsule makes them more cheerful,
more mellow, more self-assured (page 41). Now the same scientific insights into the brain that
led to the development of Prozac are raising the prospect of nothing less than made-to-order,
off-the-shelf personalities. For good or ill, research that once mapped the frontiers of disease-
identifying the brain chemistry involved in depression, paranoia and schizophrenia--is today
closing in on the chemistry of normal personality. As a result, researchers are on the verge of
"chemical attempts to modify character," writes neuropsychiatrist Richard Restak in the soon-
to-be-published "Receptors." "Most of the new drugs will be aimed not so much at 'patients' as
at people who are already functioning on a high level ... enriching [their] memory, enhancing
intelligence, heightening concentration, and altering for the good people's internal moods."

That prospect has brought psychopharmacology--the science of drugs that affect the mind--to
"the brink of revolution," as psychiatrist Stuart Yudofsky of Baylor University puts it. It is a
revolution propelled by three advances. First came the theory that every memory, every
emotion, every aspect of temperament originates in molecules called neurotransmitters. These
chemical signals course through specialized circuits in the brain. Research on brain chemistry starting in the 1940s produced lithium, Valium and other psychoactive drugs, which correct chemical imbalances responsible for grave mental illnesses. Second, "brain mapping" pinpoints which areas of gray matter become active during particular thoughts or mental states. PET (positron emission tomography), for instance, is a sort of sonogram of the brain that can, among other things, trace sad thoughts to parts of the frontal cortex. Finally, researchers are identifying which neurotransmitters travel those circuits. For example, too much of the neurotransmitter dopamine in the brain's emotion centers, and too little in the seat of reason (diagram, page 39), seems to cause suspiciousness--raving paranoia and maybe even a habit of wondering if the plumber overcharged you.

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Major mental illness wasn't always linked to personality disorders. But according to the model of the mind emerging in the 1990s, mental disease differs from endearing quirks only in degree. Personality disorders arise from subtle disturbances in the same systems that produce serious mental illnesses, argues Dr. Larry Siever of Mount Sinai School of Medicine in New York. "Someone just barely able to restrain his impulsive actions wouldn't [seem] psychotic," says Siever. "But he could act rashly"-habitually ducking into a movie instead of going to work, or buying unseen property in Florida on a whim.

As neuroscientists learn what chemicals cause which personality traits, the temptation to fool around with nature will be irresistible. The drugs that perform the mental makeovers are supposed to have no serious side effects and not cause addiction. But more than 40 years of psychoactive drugs has proved that nothing is without hazard (at first, Valium, cocaine and nicotine were not thought to be addictive, either). "If someone takes a drug every day for four years because it makes him feel or work better, something may happen that we don't know about," warns psychiatrist Solomon Snyder of Johns Hopkins University. That caution, however, has a difficult time standing up against the Faustian power of the new drugs. "For the first time in human history," says Restak, "we will be in a position to design our own brain." Some of the targets:

Of all the traits that bedevil humans, shyness may be the most hard-wired into the brain. About 20 percent of people start life with neurochemistry that predisposes them to be shy, concludes Harvard University psychologist Jerome Kagan; the other 80 percent become shy or outgoing because of life's experiences. Now scientists may have figured out how biology becomes
destiny. An inhibited child seems to be born with what amounts to a hair-trigger brain circuit: compared with other children, it takes much less to stimulate his amygdala, a small cashew-shaped structure deep in the brain that helps control heart rate and perspiration. No wonder shy infants squirm and cry: even mild stress makes their hearts pound and their palms sweat. In addition, inhibited children may have excessive levels of the neurotransmitter norepinephrine, a cousin of the fight-or-flight chemical adrenaline: just walking into kindergarten for the first time produces as much stress as a gladiator's facing the lions. "I think the time will come when we will know exactly the chemical profile of the temperamentally fearful child," says Kagan. "Then pharmacologists could work on very specific cures."

In some people, shyness is not a primary trait but instead a means of coping. "So much of social interaction is based on unspoken rhythms and pacing," says Mount Sinai's Siever. "That people who don't get those beats often feel left out and alienated"--like the woman who can't tell from body language that the man she's chatting with wants to flee. Society perceives her as slightly strange; she responds by withdrawing. Siever suspects that suspiciousness and an inability to process the information contained in the rhythms and cues of social interaction arise from an oversupply of dopamine in the brain's emotion-control room and a shortage in the more rational cortex.

One jobless, fiftyish man seemed to fit this description perfectly. He lived alone, filled his days with crossword puzzles and TV, and "worried that others were making fun of him," says Siever. Like all of Siever's patients, he was seriously ill. Siever suspected, based on biochemical tests, that the man's inability to understand social cues stemmed from a dopamine imbalance. The antidepressant Wellbutrin, which stokes the cortex with dopamine, seemed to help: the man felt sharper and "more activated" (though a back disability kept him from working). Still, scientists caution that what works on the seriously ill might have no effect on someone who decides to cure her lack of social grace with a pill when all she needs is a crash course in etiquette.

Shyness can also grow in the shadow of hypersensitivity, the tendency to fall into a deep funk over even an innocuous rejection. For years, psychiatrist Donald Klein of Columbia-Presbyterian Medical Center in New York had noticed something strange about this funk: it closely resembled the reaction of an amphetamine user suffering withdrawal symptoms. That sparked a bold theory. "The brain is normally making its own stimulant." which keeps people on an even keel, and even makes them outgoing, says Klein. Some people who embarrass easily and cower at the very thought of rejection may do so because their brain does not pump out enough stimulants. They become physically pained by rejection just as a speed freak is
physically pained by going cold turkey. "Recently we have shown-that we can treat this by preserving the balance of stimulants in the brain and so blocking the withdrawal symptoms," says Klein. He and Columbia's Michael Liebowitz give hypersensitive patients Nardil, the trade name for a substance that blocks the destruction of the brain's natural uppers. As a result, it restores a healthy chemical balance in the hypersensitive mind. "With pills twice a day you usually see results in six weeks." says Klein.

Just about everyone has, at one time or another, succumbed to the impulse to buy those goodies at the supermarket checkout. In more severe forms, such impulsive behavior expresses itself as kleptomania and other mental illnesses whose sufferers act first and think second. But mild or severe, impulsivity may arise from the inability to learn that behaviors have consequences, like punishment, and so must be controlled or modified.

Depending on where the impulsivity comes from, psychopharmacologists may soon know how to stifle it. As a teenager, did you repeatedly stay out until dawn despite getting grounded for it every times Are you prone to doing what gets you fired? The problem may stem from too little serotonin, the chemical whose job it is to censor behavior that previously led to punishment, says Siever. Shortages of serotonin in the frontal lobes and in the brain's limbic system, where emotions come from, also seem to lift the lid off impulses. In this case, the dearth of serotonin seems to have the same effect as a shortage of ink in which to write life's lessons: the person is unable to connect disagreeable consequences with what provoked them. Or the problem may simply be an inept working memory. (But Mom, I forgot you wanted me home!) Working memory stores information while the mind considers whether it is worth keeping and how to file it. Working memory falters without enough dopamine.

There's a final suspect in impulsivity. Noticing everything can be as debilitating as noticing nothing. Norepinephrine tells the mind what's important by, in effect, putting a chemical red flag on it to say, "Look at this!" In normal people that system kicks in when, for instance, a lion is charging. But in people with too much norepinephrine everything gets pumped up. Every perceived slight from a co-worker demands a response, every twinge of desire becomes an irresistible urge to buy.

If impulsives think about their actions too little, obsessives think about them too much. When Mother double-checks that the sleeping children are indeed breathing, and when she's a stickler about dirt on the carpets or grime in the kitchen, she is being mildly compulsive; when she checks 100 times, vacuums 20 times a day and goes through Fantastik like an alcoholic through
rotgut, she is manifesting obsessive-compulsive disorder. Sufferers seem unable to get a sense of completeness from any action, like scrubbing the bathtub a mere once. Brain imaging is now showing such obsession in living color. PET scans of a patient touched with a dirty rag-cleanliness is a typical obsession--show a response like a broken record. Signals travel between three structures in the brain stem-the prefrontal cortex, the basal ganglia and the thalamus--endlessly. in normal people, the signal stops after one orbit thanks to a new message, screaming, "The floor is clean already!" "Lots of people have milder variants of this," says neuroscientist Lewis Baxter of the University of California, Los Angeles. "They check the stove two times, though not 102. They say that intellectually they know the stove is OK, but they can't get the emotional boost that says, 'Hey, it's working'." Baxter believes that even mild compulsiveness might succumb to drugs that change the brain's regulation of serotonin. In fact, Prozac is about to be approved for use against obsessive-compulsive behavior. The great unknown is whether Prozac and other powerful drugs will work on milder forms of severe disorders.

The neural pathways to anxiety exist because early humans who got a little nervous at the sight of, say, a crouching saber tooth had a survival edge over more laid-back tribesmen. Now, in the age of anxiety, many people would just as soon give back this legacy of natural selection. At the National Institute of Mental Health, Philip Gold is figuring out how. He traces stress to the circuit responsible for the fight-or-flight response. In the chronically anxious, he says, "it turns on, but it doesn't turn off." Antidepressants called tricyclics, which throttle back levels of the fight-or-flight norepinephrine, seem to still the perpetual arousal in the circuit.

A shortage of norepinephrine seems to rob people of the ability to pay attention to what's important, and only to what's important. Sally Jackson, the forty-something owner of a Boston public-relations firm, knows the problem well. She had often felt unfocused, so last winter she began taking Ritalin, a stimulant that increases the availability of norepinephrine. Although Ritalin is best known as the controversial medication for children diagnosed with attention-deficit disorder (ADD, alias hyperactivity), adults are now taking the yellow pills to improve their concentration. "Without it, I would sit at my desk for hours and get nothing done," says Jackson, who believes she has ADD. "But once I started Ritalin, every proposal I wrote, we won the account. I'm better on deadline and it keeps me focused on one task at a time." She swallows one pill in the morning and another if she hits a 3 p.m. lull.
Prozac to cheer you up and Ritalin to focus are merely the most prominent new mind drugs. Anticonvulsants such as Dilantin, prescribed for epileptics, turn out to reduce stress in some people. Beta blockers are heart drugs: they lower blood pressure and heart rate. But doctors figured out an entirely new use for them: combating stage fright. The drugs block receptors for norepinephrine; with less adrenaline igniting their brain circuits, people like oboist Stuart Dunkel, who plays for the Boston Opera, have no trouble calming performance anxiety. Before, complicated solos would make Dunkel's heart beat like a jackhammer and his breathing so shallow he couldn't sustain notes. With beta blockers, "there's a psychological release," he says. The drugs are not addictive, and Dunkel reports no side effects.

Other mind drugs are in the pipeline. One, with the tongue-tying name dexfenfluramine, seems to smooth out mood swings, especially those caused by winter doldrums and premenstrual syndrome. Naturally, it targets neurotransmitters: it keeps brain neurons bathed in serotonin longer than otherwise, explains Judith Wurtman of the Massachusetts Institute of Technology. Already used in Europe and South America as an anti-obesity drug (mood swings often trigger eating binges), dexfenfluramine has been submitted to the FDA for approval. A few weeks ago researchers at UC Irvine announced the discovery of the first drug that seems to improve working memory. The discovery sprang from work on neurotransmitters and their receptors, the shapely molecules that neurotransmitters fit like keys in locks (diagram). Researchers led by Gary Lynch found that in rats, the drug BDP binds to receptors for the neurotransmitter glutamate, which triggers neuronal changes that constitute memory. As a result, it acts like the father who lowers the basketball net for his vertically challenged child, reducing the amount of stimulation neurons require to form memories. If BDP works in people, the history lesson that once took hours to learn would take mere minutes. An Irvine-based start-up, Cortex Pharmaceuticals, Inc., plans to test BDP's safety.

Who could criticize a drug that stamps the rules for long division into your child's head after a single lesson? As psychiatrist Daniel Luchins of the University of Chicago points out. society accepts plastic surgery (albeit with some jokes): "If we have something that made people unshy, are they obliged to stay shy because of some ethical concern? What's the difference between' 'I'm unhappy because I don't like my looks' and 'I'm unhappy because I'm shy?'"

For openers, one's core being is defined more by character traits than by the shape of one's nose. Just ask Cyrano. And not everything we feel, let alone everything we are, is shaped by too much or too little of some polysyllabic brain chemical. Yet as society moves ever closer to minds-made-to-order, the pressure on those who cannot, or choose not to, give their brain a
makeover becomes intense. Some colleagues, and competitors, of Ritalin-popping executives feel themselves at a disadvantage, like rules-respecting sprinters facing a steroid user. Will guidance counselors urge parents to give their kids memory pills before the SATs? Will supervisors "suggest" workers take a little something to sharpen their concentration? The prospect of pills to make the dour cheery, and the tense mellow, calls into question the very notion of the self--is it truly the "self" in any meaningful sense if it is as easy to change as a bust measurement? "The brain is where our soul and spirit lie," says Harvard's Kagan. "People are very threatened by this."

Perhaps most worrisome is the idea of sandpapering away personality traits that not only make us individuals, but which evolved for a good reason. Anxiety, for instance, "probably evolved in tandem with the evolution of the human brain," writes Restak. Blunting that edge has a price. And just as physical pain keeps us from burning our flesh, perhaps mental pain, like that brought on by the death of a child, serves a purpose-one that is defeated by a pill that soothes when one should instead be raging. Shyness has also served civilization well. Some of history's great thinkers and creators--T. S. Eyelet, Emily Dickinson, Anton Bruckner--were--shy. "Inhibited children tend to wander off into vocations like music, literature and philosophy," says Kagan. A society that uses drugs to induce conformity does so at its peril.