DISABILITY ANALYSIS IN PRACTICE

Framework for an Interdisciplinary Science

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CHAPTER 2

Psychopharmacology and the Disability Analyst

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The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.

—William Osler

Introduction

This chapter is written to provide a pharmacologist's perspective on some of the complexities of the field and to warn of pitfalls of over-simplification that can confound the non-pharmacologist, especially in the forensic domain. In particular this article will attempt to address the phenomenon of rare or 'unusual' effects of psychoactive drugs, including behaviorally toxic effects, and clarify some of their mechanisms. Pharmacology as practiced by pharmacologists is a "hard" science, based on empirical research, yet as viewed by certain other professions not schooled in its disciplines, it is often seen as an 'art,' shrouded in mystery. The recent and momentous *Daubert* decision (which lawsuit concerned the alleged toxic effects of a sedative drug combination), emerged from a consideration of such 'rare drug effects' and the 'opinions' of 'experts' regarding causation of damage. *Daubert* utterly changed the standards of forensic evidence for use in court proceedings in the United States of America (Federal Judicial Center, 1994). In *Daubert*, it was ultimately conceded that the expert's standard of reliance upon *"facts,"* which hitherto was based upon a standard holding that the *"fact"* must be *"generally accepted as true"* by the expert's profession, was forensically inadequate. General acceptance, *Daubert* concluded, does not ensure that the *"fact"* is scientifically valid, unless this fact is actually supported by the findings of valid scientific research.

The Scope of Neuro(Psycho)pharmacology

Psychopharmacologists (or neuropharmacologists, the terms are slowly becoming interchangeable) are commonly consulted on questions regarding psychoactive drug pharmacology, pharmacokinetics (tissue levels, including blood) or pharmacodynamics (effects). For everyday questions regarding the formulation or prescription of psychoactive drugs or common drug interactions, the pharmacist is the practitioner's first choice in the search for information. For questions regarding the typical effects of such drugs, if these are prescription drugs, the psychiatrist is often the first port of call. The neuropharmacologist, however, is usually the best source of information regarding weird, exotic or unusual drug actions, drug interactions or effects. In certain esoteric areas of enquiry such as the drug effects of certain foods, drug-food interactions, drug-metabolism interactions or nonprescription drug (including drug of abuse) matters, the neuropharmacologist is often the only professional resource available.

The majority of neuropharmacologists work for industry, researching and developing new psychoactive drugs and conducting research on folk medicines, natural products and so-called 'New Chemical Entities' (NCEs) in pursuit of novel treatments. A large number perform research in university laboratories and a smaller proportion practice independently, either within the field of some other profession—such as psychology or toxicology—or alone, as pure or applied practitioners.

In clinical medicine, we don't often need to understand inter-individual variation or idiosyncratic drug response. If the response obtained is not the response desired, we merely change the dose or the drug prescribed. However, there are circumstances where we simply have to know and understand what happened when a drug was administered, when changing the prescription is not enough. Examples of such circumstances include those occasions when drug administration caused adverse consequences, such as behavioral toxicity or death. Usually, these consequences are unintended on the part of the prescriber or individual drug taker. Often, they are rare idiosyncratic responses to drug consumption that appear to defy explanation or whose explanation is sufficiently outside the mainstream of common knowledge that expert pharmacological consultation is required.

As might be expected, such circumstances often fall into the "forensic" arena, where a tribunal, disability board, civil, criminal or coroner's court or other statutory litigating body is attempting to judge the circumstances or consequences of the suspected drug effect. For this reason, in practice, a proportion of a consulting neuropharmacologist's time is spent in forensic consultation on the investigation of alleged untoward drug effects and their consequences.

The Variabilities of Drug Effect

"Take two aspirin and call me in the morning" is a common and reasonable prescription. For the majority of the population, this dose of this drug will be appropriate and its benefits will outweigh its risks. For a very small proportion of the population, however, those who suffer **idiosyncratic drug sensitivities**, either this drug or this dose will be wrong, and may be dangerously wrong. It is the purview of the pharmacologist to study such rare populations in the context of the population as a whole—hopefully (with 'ethical drugs' as commercial prescribable therapeutic drugs are called) before the drug is released by the manufacturer into the market and the general population. At certain doses, under certain conditions and in certain people, aspirin may induce dangerous asthma attacks, anaphylactic reactions, hemorrhage, gastrointestinal problems and even death.

The problem with idiosyncratic drug effects is their rarity. Only in very large populations will a small number of drug-takers experience adverse effects sufficiently profound to be noticed. When such effects are observed they may not be associated with the drug's causation, particularly in the premarket approval process that precedes commercialization. The pharmaco-epidemiologist is usually the first to notice rare adverse occurrences in the wider post-marketing surveillance, which begin to form a pattern for the research pharmacologist to examine in greater detail mechanistically in the laboratory. The recent Phen-fen debacle is a case in point. Pharmacologically, dexfenfluramine should not be expected to have a toxicity profile qualitatively different from its older racemic form (fenfluramine), which contains a mixture of both dex(tro)- and laevo-forms of the molecule, the dextro form being more biologically active, and has been on the market for years. The only advantage of pure dexfenfluramine is that it refreshes the expired patent on a successful drug, allowing the company a market monopoly for a time. The drug has now been withdrawn because dangerous and potentially lethal adverse effects were noted in post-market surveillance. We are not surprised to learn that these effects seem to be the same as those known to be caused by racemic fenfluramine itself. One ignores these general pharmacological principles at one's peril.

The varieties of drug effect are due to many independent variables, including illness—of the body or mind—and including race and gender, prior drug exposure and experience, age, weight, diet, other drugs and foods coadministered and medical and psychological problems or peculiarities of metabolism. Such peculiarities may not necessarily be 'illnesses' in the general sense of the word and may not be noticed by medical practitioners. Sufferers of Gilbert's syndrome, for instance, either inherit or acquire a deficiency in their ability to glycosylate compounds in the liver associated with the metabolic pathway that utilizes Cytochrome P_{450}. The gene controlling the activity of this cytochrome is called P450 2D6. Gilbert's syndrome "sufferers" have no outward disease as such, just a tendency to jaundice that is medically trivial, but they may have a profoundly altered ability to metabolize certain drugs, including acetaminophen and benzodiazepines (Herman *et al.*, 1994). Another example is the histamine-releasing action of opiates. This action is not a true "allergy" since it is entirely caused by the normal pharmacological action of the opiate and does not directly involve the immune system (histamine is the principal mediator of opiate action on the dog gut muscles, for instance) and to some degree occurs in everyone who takes these drugs. However, the opiate responsiveness of certain rare individuals is exquisitely histamine-sensitive and can

be life-threatening. Other sources of pharmacological variability, as described above, are general to the user's age or race or gender and hence not truly 'idiosyncratic,' although they may contribute to idiosyncrasy.

Racial differences in the effects of psychoactive drugs should properly influence choices made in the prescription of psychopharmaceuticals and the drug therapy of mental disorders. African Americans respond better and more rapidly than white western Europeans to tricyclic antidepressants, for instance, an effect that is apparently related to the higher serum concentrations achieved over the dosing schedule (higher ratio of serum concentration to dose) in African versus white races (Silver, 1993). Likewise, the metabolic conversion of haloperidol to reduced haloperidol determines in part its effectiveness. The ethnic Chinese achieve higher haloperidol concentrations per dose per dosing schedule than do non-Chinese, whereas African and Caucasian haloperidol pharmacokinetics seem to be equivalent (Jann, 1993). Since the upper therapeutic plateau range for haloperidol concentration in serum is believed to be roughly 20-25 ng/ml, dosages greater than 30 mg/day should not be necessary in Chinese patients, and dosages greater than 50-60 mg/day should not be needed in non-Chinese patients (Kirch *et al.*,1985; Volavka & Cooper, 1987; Jann *et al.*, 1993)

Gender differences also account for a major source of variation of drug effect, and this is in part related to the dimorphism of the sexes' hepatic (liver) metabolism and its dependance on hormonal regulation. Diazepam is excreted more slowly in females than males, for instance, until after menopause, when this difference disappears (MacLeod, 1979). A recently discovered gender difference whose mechanism has not yet been fully explored is the greater sensitivity of women than men to the kappa opioids nalbuphene and butorphanol (Gear, 1996) and the greater pain relief these treatments afford women. To the extent that women have a greater proportion of fat to muscle, they also have different Apparent Volumes of Distribution (V_d) from men. V_d is a proportionality constant which describes the amount of drug in the total body relative to that in plasma at any one time. The constant is high (>1 L/Kg) for drugs with high concentrations in tissues compared with plasma. Women have a slightly smaller V_d for ethanol, for instance (0.7 L/Kg) than do men (0.73 L/Kg). Furthermore, the V_d for ethanol changes in men with regular consumption (to 0.88 L/Kg), whereas that for women does not (Ellenhorn & Barceloux, 1988), leading to different temporal patterns of intoxication on ethanol in the two genders. Gender differences in V_d and changes in V_d with chronic use are only one of many sources of inter-gender variability in drug response. A major determinant of variability in women is due to the influence of the menstrual cycle on drug parameters, and this is reviewed below.

The effects of age are quite well studied as a determinant of drug action, of pharmacokinetics and pharmacodynamics, and for this reason the prescribing of drugs to the very young or the very old is best left to practitioners who have special familiarity with the age group in question. Pediatric pharmacologists are thus aware of the determinants of altered drug responsiveness in infants and children that distinguish them from the "average" adult. These determinants affect every stage of drug action—absorption, distribution, end-organ effect and elimination. Thus, oral absorption of some neuropharmacological drugs such as diazepam, clonazepam, phenobarbitone, sodium valproate, ethosuxamine and imipramine may be more rapid in children than in the adult (Morselli, 1997). Furthermore, drug distribution is greatly different in children compared with adults, in part because of the child's proportionally greater extracellular fluid volume. Adult values for extracellular fluid volume

are reached around 13 to 15 years of age, whereas total body water increases slightly around puberty after which time a gradual decrease occurs throughout adult life (Friis-Hansen, 1961, 1971). It follows, therefore, that for highly water-soluble drugs without extensive tissue binding, calculating dosage on the basis of extracellular water is more rational than on a body weight basis. Additionally, the degree to which the drug is bound or unbound to plasma proteins determines its biological availability for absorption by the brain and other tissues of the body and changes in protein binding of the drug occur over the life-cycle. These changes occur not only as the albumin concentration of the plasma proteins changes, but also as the binding capacity of the proteins changes. A component of this variation parallels changes in the body's free fatty acid and bilirubin levels, since these compete with globulin and albumin for protein binding sites occupied by drugs. Taking an example from the case of phenobarbitone: the fraction of unbound drug (which is available to be distributed to, and to act on, the brain), which is already high in newborns (60-65%), may reach around 70% or so in the presence of hyperbilirubinemia. Likewise, the fraction of unbound phenytoin in the plasma of infants, which is already twice that of adults, is increased to three times adult values in the presence of high bilirubin levels (Ehrenbo *et al.*,1971; Rane *et al.*, 1971). For these and other reasons, the Apparent Volume of Distribution (V_d) of a drug changes over the life-cycle, generally increasing but in some cases decreasing with the child's maturation. A drug's elimination rate likewise changes over the life-cycle, generally increasing with age and with growing maturity of metabolic and eliminative processes. The overall clearance rate is a product of its component processes and changes accordingly with age. Thus, diazepam has a half-life ($t_{½}$) of 22-46 hours in neonates, decreasing to 10-12 hours in infants, then increasing to 15-21 hours in children and returning to 24-48 hours in adults.

As with the earlier years of life, special pharmacological considerations apply to the elderly. Total body water and lean body mass fall with advancing age, the effects of which alterations are initially concealed by an increase in the proportion of fat in the body. Metabolic rate also diminishes with increasing age (Crooks *et al.*, 1976) and the $t_{½}$ of certain drugs metabolized preferentially by hepatic (liver) metabolism become prolonged—such as antipyrine, phenobarbitone, acetaminophen and diazepam. However, the elderly's V_d is also increased, such that plasma clearance of the drug may overall appear unaltered. By far the most profound difference that aging imposes on drug variability is an increased sensitivity of the end-organ, which, in the case of neuropharmacological drugs is, of course, the brain. The reaction of elderly patients to barbiturates is the most well-known (Bender, 1964). The elderly respond to these drugs with a spectrum ranging from mild restlessness to frank psychosis in a significant proportion of the age group. The difference between adult and elderly response to the barbiturates is so very different that it must be described as qualitative—it cannot be accounted solely on the basis of increased plasma level.

The linear passing of years is not the only influence of time upon drug action and adverse effects: **Chronopharmacology** is the science of rhythms and their influence on drug action. Some chronopharmacological rhythms are diurnal and reflect the daily cycle of wakefulness and sleep. This is related to urine acidity and drug excretion, whilst other daily rhythms reflect cycles of drug metabolic activity as these change within the day (infradian rhythm) or the year (circannual rhythm) and are influenced by endocrine cycles and by cycles in the responsiveness of end-organ tissues (called "**chronoesthesy**"). The most common cycle influencing drug action is the menstrual cycle in women. Caffeine metabolism appears to be

slowed, for instance, in the late luteal phase compared with follicular phase (Lane *et al.*, 1992), an effect attributed to progesterone level. Recent studies on the clearance of the related drug theophylline seem to indicate that this drug's half-life is significantly shorter in the menstrual than the follicular phase of the cycle (Nagata *et al.*, 1997). Alcohol pharmacokinetics likewise change somewhat over the course of the menstrual cycle and elimination rate has been reported to increase by about 14% during the luteal phase, compared with other stages of the cycle (reviewed by Lammers, 1995). Attempts to account for the changing efficacy of lithium over the course of the menstrual cycle have not, thus far, found any pharmacokinetic correlation with cycle phase (Chamberlain *et al.*, 1990), suggesting, therefore, that the variability is one of chronoesthesy, or end-organ sensitivity.

The timing of drug administration is thus critical in the mediation of both beneficial and adverse effects. Lithium, for example, is regulated by diurnal cycles. A study by Lambinet *et al.* (1981) manipulated the administration schedules of depressed patients treated with lithium carbonate. These authors compared three schedules: (i) two thirds of the daily dose at 08:00 h and the remaining third at 12:00 h *or* (ii) equal doses at 08:00 h, 12:00 h and 20:00 h, *or* (iii) one third of the daily dose at 12:00 h and two-thirds at 20:00 h. The latter schedule reduced lithium nephrotoxicity (measured by creatinine and urea clearance) and reduced the large-amplitude circadian rhythm of urinary lithium excretion. Not only, therefore, does target tissue responsiveness to a drug vary with time of day, but the pharmacokinetics of the drug are time-of-day dependent. This was noted twenty years ago for ethanol, by Sturtevant and colleagues (Sturtevant *et al.*, 1976, 1976 a, 1978). Their studies showed that the rate constants of ethanol kinetics (change of blood levels following dosing) described a sinusoidal rhythm that varied from day to day—presumably because the periodicity of the variation was not phase-locked to the 24 hours of our "day." A similar rhythm to the pharmacokinetics and dynamics of antihistamines and other sedative and psychoactive drugs has been described (Reinberg, 1990, for review)

Thus, often overlooked in daily medical practice are the profound pharmacobiological determinants of inter-individual variation. For the vast majority of the population this neglect has little or no clinical consequence, but in those cases where forensically-relevant adverse effects occur, these variables must necessarily be taken into account.

Interaction of History and Predisposing Mental Illness on Drug Effect

In the prescription of psychotherapeutic drugs, pre-existing psychopathology or mental illness constitutes the reason for the prescription. Neuropharmacological drugs are therapeutic precisely because they interact with the disordered brain chemistry that underlies the mental illness being treated. Tricyclic antidepressants are, for instance, not mood elevating in individuals who are not depressed to start with.

The drug-taker's pre-existing mental disorder thus greatly influences the drug effect, not only the desirable but also the adverse effects of drugs. Bipolar patients, for instance, whose moods cycle between extremes of depression and mania, usually suffer greatest during the depressive phase of the illness and frequently present to the prescriber in this condition. If not properly diagnosed a bipolar patient may wrongfully be labeled unipolar depressive therefore. However, tricyclic antidepressant drugs, which are most useful in unipolar depression

treatment, have the unfortunate property of "switching" a proportion of the bipolar depressive population into the manic or hypomanic stage of the illness, often with catastrophic consequences (Goodwin & Jameson, 1990). Less well appreciated is the fact that although bipolar patients may feel subjective relief of their depression of mood in response to illicitly consumed psychostimulants, these drugs exacerbate mania. Particularly in regard to the non-prescribed drugs of abuse, it is sadly all too common for the pre-existing state of the user to be ignored in evaluating the effects of drugs on their brain and behavior.

"Set" and "setting" of drug use greatly influence the overall effect, and pre-existing mental history is an important factor of **"set."** Others include those historic and predispositional aspects of the user's past that interact with drug action. Factors of **"setting"** include the situation in which the drug taking occurs and are—or can be—medical, dietary, psychological or environmental. Examples of environmental setting influences include temperature and also barometric effects due to altitude above or depth below sea level (ethanol intoxication is subject to modification by barometric pressure, for instance, as scuba divers are well aware). Factors of psychological setting include the degree of perceived threat level or comorbid anxiety attending the taking of the drug.

Factors of **set** also include the users' drug-taking history. **Tolerance** is a well-known example of the persistent effects of prior, historic, drug use: whereby prior drug use decreases the effectiveness of subsequent drug use. Less well appreciated is the fact that tolerance develops and dissipates at different rates for each of the different effects of a single drug and the rate of development and duration varies widely between drugs. Barbiturate tolerance lasts for many years, for instance, whereas heroin tolerance to respiratory depression is lost quite rapidly after the last dose is administered, which accounts in part for the large number of accidental fatal overdoses ascribed to this drug's abuse. Tolerance development in each drug class is different for a number of reasons characteristic of the drug. **Metabolic tolerance** caused by hepatic induction of degradative enzymes takes longer to develop—hence is associated with chronic drug use—and is longer lasting. Sub-acute tolerance, such as that induced at the end organ, known as **tissue tachyphylaxis**, a form of **tissue tolerance** mediated at the drug receptor itself, tends to be short-lived and ephemeral.

Some drug classes including the psychostimulants, amphetamines and cocaine, induce tolerance to certain of their effects yet simultaneously induce **reverse tolerance**, otherwise called **sensitization**, to others. Reverse tolerance is believed to account for the phenomenon of **kindling** whereby chronic psychostimulant abusers progressively acquire increased sensitivity to the psychosis producing (psychotogenic) effects of chronic treatment. Thus kindled, the brain is more sensitive to limbic seizures as can be demonstrated in laboratory models and in the persistent increased vulnerability of the street drug abuser to psychotic decompensation (Post, 1975; Post & Kopanda, 1976). Other historic variables that influence drug taking outcome include **state-dependent memory**: things learned or emotions experienced, or both, whilst under the influence of a drug will later be best recollected when under the same drug influence (Ross & Schwartz, 1974).

It is particularly in regard to the drug abusing population that the perspective of the neuropharmacologist differs most significantly from the mainstream therapeutic psychological professions. To the psychologist or psychiatrist, a drug abuser is invariably considered a mentally disordered individual who is also engaged in drug abuse. The epithet "dual diagnosis" is applied to such people. Clinically, the significance of the dual diagnosis concept is

that in withdrawing such people from their drug abuse and attempting to restore them to long-term health, their underlying mental disorder must be taken into account therapeutically. The influence of the patients' underlying disorder upon the nature and quality of the drug effect itself, the addiction, and its organic psychopathology is—quite properly—of less interest to the psychologist than the impact such disorder will have on the cure. To the neuropharmacologist, however, who is interested in studying the effects of drugs on brain, mind and behavior, the focus of their interest is more clearly on the contribution of the subject's underlying disorder on the expression of drug-induced derangements.

In everyday clinical practice such differences in viewpoint regarding the drug abuser have little practical significance, since both professional perspectives agree that therapeutically the drug abuser must abstain and remain abstinent from the abused drug. In the forensic sphere, however, the pharmacologist is often more interested in understanding how the drug abuser got himself into such a state of neurochemical derangement than in how to get him out of it. Diagnosis rather than treatment is the goal, in such cases. This naturally follows from the pharmacologist's scope of practice, which seeks to better our understanding of inter-individual variation in drug response.

Influences of Pre-existing Mental Illness or Psychological Idiosyncrasy

Pre-existing mental disorders influence the effect of psychoactive drugs in several ways. Firstly, certain predispositions are believed to underlie the individual's drug appetite and to influence the acquisition of a drug abuse habit. Secondly, pre-existing mental disorders or psychological idiosyncrasies profoundly influence both the subjectively desirable and undesirable effects of drugs, including drugs of abuse.

Clinical work with narcotic and cocaine addicts has provided us with compelling evidence that the drug an individual comes to rely on is not a random choice. Although addicts experiment with multiple substances, most prefer one drug or specific drug combination. Weider and Kaplan (1969) referred to this process as the *"drug-of-choice phenomenon,"* Milkman and Frosch (1973) have described it as the *"preferential use of drugs"* and Khantzian (1985) has called it the *"self-selection process."* Each of these authors are trying to explain a common phenomenon: abusers of drugs suffer with certain overwhelming affects and with cognitive, relationship and behavioral disturbances and the short-term use of their drug of choice *subjectively* and selectively helps them to combat the psychic pain of these disturbances. It must be emphasized, however, that no single type of mental disorder predisposes the user to a particular drug appetite—rather, many prodromal (preceding) courses lead to a common subjective relief with a particular drug of abuse.

Opiate Abuse Although opiate drugs (those of the morphine class, including heroin) are primarily known for their relief of pain, stress and dysphoria, there is evidence that the user's initiation occurs when they subjectively perceive the anti-rage effects. Khantzian (1985) bases this opinion on observations of over 200 addicts whose histories revealed lifelong difficulties with rage and violent behavior predating their addiction, often linked to intense and unusual exposure to extreme aggression and violence in their early family life

and the environment outside their homes. These experiences include being both the subject and perpetrator of physical abuse, brutality, violence and sadism. Such patients repeatedly describe how opiates help them to feel normal, calm, mellow, soothed and relaxed. Khantzian also observes an impressive reduction in their restlessness and aggression in group treatment, especially manifested in their abusive and assaultative use of obscenities, which subsides as they are stabilized on methadone.

Stimulants The varieties of predisposing appetite typologies are greater for the psychostimulants, including cocaine and the amphetamines, than the opiates. Although no conclusive evidence has yet been amassed, there do seem to be three premorbid types that are preferentially predisposed to stimulant abuse:

1. pre-existent chronic depression
2. hyperactive, restless syndromes due to subtle brain damage or attention deficit disorders
3. cyclothymic or bipolar illness.

The psychic pain of these conditions are to some extent each subjectively relieved by psychostimulant drugs. Indeed, both cocaine and the amphetamines were at one time prescribed for treatment of depression and the amphetamines are still prescribed for attention deficit hyperactivity disorder, with remarkable clinical effectiveness both subjectively and objectively.

Adverse Effects and Predisposing Mental Illness

It is in the interpretation of adverse outcomes of drug treatment and drug abuse that a consideration of the contributions of pre-existing mental illness or psychological idiosyncrasy becomes paramount. Examples of adverse effects, often considered 'paradoxical,' can be found in all drug classes.

Taking the benzodiazepine family as an example, these drugs are normally considered tranquilizing, calming and anxiolytic, yet so-called 'paradoxical reactions' to benzodiazepines include depression, gross behavioral disturbances, hostility, aggression and rage.

Depression induced by benzodiazepine drugs may represent an exacerbation of pre-existing endogenous depression or in some cases may be related to idiosyncratic cerebrovascular problems. Reviewing widespread reportage of this paradoxical depressive response to benzodiazepines, Hall and Zisook (1981) have noted that the exacerbation often leads to suicidal ideation and occasionally to successful suicide. Curiously, some depressed users of benzodiazepines self-administer them in an abuse fashion even though these drugs have no inherent antidepressant properties *per se*. Presumably the benzodiazepine is subjectively attractive to those suffering anxious or agitated depression because of the drug's anxiolytic properties, satisfying their immediate needs at the expense of their underlying problem.

Gross behavioral disturbances have been reported to occur "paradoxically" in response to benzodiazepines, ranging from agitation to paranoia to psychosis, confusional states, manic and hypomanic responses, extreme garrulousness and hallucinations, vivid dreams and nightmares.

Since the benzodiazepines normally exert anxiolytic and tranquillizing effects, the provocation of violence, hostility and rage in some individuals does indeed seem superficially paradoxical. Yet reports of such effects are not uncommon (Hall and Zisook,1981), and it has become obvious that in such individuals the rage reactions are not in fact paradoxical but are rather predictable behaviors which occur only in a sub-population of patients. This subset seems to have a predisposition for explosive dyscontrol, and a past history of poor impulse control which interacts with the drug's pharmacological properties, thereby unleashing the patients' restrained hostility. Earlier work by Salzman *et al.* (1974) supports these findings empirically and has additionally found that the hostility can more easily be provoked when the environment is structured to produce situations of interpersonal frustration. Covi and Lipman (1977) working with moderately depressed female outpatients found that diazepam (valium) caused overt behavioral hostility in a manner proportionally related to their pre-existing hostility level.

The conclusion that benzodiazepines may induce rage in subjects with high levels of pre-existing hostility, who have personality disorders, and that such reaction is made more likely when the environment is structured to produce frustration, is of particular forensic relevance in prison populations. In agreement with this conclusion, Calvin Brown (1974) reporting on a period when it was thought beneficial to allow unrestrained use of benzodiazepines in the Utah prison system to 'tranquilize' the prisoners, found significantly increased violence during this time. He reported: *"twenty-two cases of deliberate sputum injections (a type of self-mutilation), two major riots, five minor riots, one murder, two suicides, forty-four self-mutilations, six stabbings of other individuals, eight attacks on guards and other inmates . . . it became quite obvious that the drug policy would have to be changed."*

Benzodiazepines are not alone in provoking violent rage in select individuals. The phenomenon is common to drugs which erode inhibitory controls in those whose control regulation is impaired or in whom underlying hostility is high. One special case of interest is the rare phenomenon of '**pathological intoxication,**' particularly on alcohol. In an empirical study of one hundred and thirty eight neuropsychiatric outpatients, Mungas (1983) found no relationship between substance abuse and frequency of violence, yet found a striking positive relationship between substance abuse and severity of violence. In an earlier study by Bach-y-Rita *et al.* (1971), examining a cohort of 130 patients with a chief complaint of "explosive violent behavior," it was found possible to discriminate five different sub-groups on the basis of history and organicity, of which one group, consisting of 25 patients, met the diagnostic criteria for "pathological intoxication" on alcohol. These individuals would go 'berserk' after consuming relatively little alcohol, usually had amnesia for the explosive violence, and while they were out of control they appeared to be psychotic. Both Mungas and Bach-y-Rita found organic brain damage to be common in the histories of these patients, but unlike the explosive subjects whose violence could be attributed to temporal lobe epilepsy, no clear electroencephalographic correlates could be found in the 'alcohol pathological intoxication' group (Bach-y-Rita, Lion & Ervin, 1970, Bach-y-Rita, 1971).

Drug-Induced Organic Psychoses

Organic psychoses are common to chronic high-dose psychostimulant abuse and to chronic hallucinogen abuse. Resembling acute paranoid schizophrenia in many respects,

considerable evidence links heightened vulnerability to the experience of these protracted psychotic syndromes to various pre-existing conditions.

Chronic Psychostimulant Abuse: Cocaine and the amphetamines differ significantly in regard to the severity and chronicity of the toxic organic psychosis resulting from their chronic abuse. Both cocaine and the amphetamines share an affective similarity—in that both drugs elevate mood, dispel dysphoria, and their absence, on drug withdrawal, precipitates depression. The psychostimulants are therefore particularly desirable for those suffering retarded depression, although less so for those suffering agitated depression.

Sustained amphetamine psychosis lasting days to weeks has been described in individuals with no apparent premorbid major mental illness who develop this psychosis whilst taking the drug and in whom the psychosis persists for weeks after the drug is discontinued. The original report of the phenomenon (Young & Schoville, 1938) was of a case where the psychosis persisted for over a year. In contrast, cocaine commonly induces a rather similar psychosis—resembling acute paranoid schizophrenia—but this is much less protracted after drug discontinuation. Usually the symptoms dissipate after the "crash phase" of the withdrawal. In a study by Satel *et al.* (1991) of one hundred cocaine-dependent males, none reported cocaine paranoia extending beyond the crash phase. Conversely, in a series of 66 cocaine-using schizophrenic and bipolar patients admitted for disorganized behavior, all remained psychotic for at least 42 days. Furthermore, their psychotic symptoms required significantly higher neuroleptic doses to treat than had been the case prior to their cocaine abuse—that is, cocaine exacerbated their underlying psychotic disorder and induced psychotic decompensation

Another study on "psychosis proneness" to cocaine intoxication (Satel & Edell, 1991) found that individuals with a 'proneness' to cocaine psychosis can be identified in several ways. These neurobiologically vulnerable individuals had elevated scores on the Perceptual Aberration Scale and the Magical Ideation Scale—two measures of abnormal thinking. Most importantly, they found that users who experience acute transient paranoia when using cocaine were most likely to become chronically psychotic on protracted cocaine abuse.

Although chronic abuse of amphetamine more regularly induces a paranoid schizophreniform (schizophrenia-like) psychosis than does abuse of the shorter-acting cocaine, some individuals are uniquely and "abnormally" vulnerable, predisposed, to amphetamine psychosis. Those with paranoid and psychotic disorders are obviously vulnerable, but high-functioning borderlines can readily be decompensated and their kindled (Post & Kopanda, 1976) or heightened vulnerability to subsequent psychosis is believed to be long-lasting (Graff, Baer & Comstock, 1977; Tomiyama, 1990). Nevertheless, cases have been reported (Gold & Bowers, 1978) where no obvious predisposing psychopathology could be found

Organic Hallucinogen-Induced Psychoses

There are many varieties and pharmacological families of hallucinogens, differing from each other mechanistically and in other ways, a complete exposition of which lies outside the scope of the present chapter. To further complicate our understanding, the effects of the hallucinogens, both desirable and undesirable, are exquisitely sensitive to the setting of their use, and acute adverse effects can easily result if the environment in which the drug user finds himself

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Chronic Psychostimulant Abuse: Cocaine and the amphetamines differ significantly in regard to the severity and chronicity of the toxic organic psychosis resulting from their chronic abuse. Both cocaine and the amphetamines share an affective similarity—in that both drugs elevate mood, dispel dysphoria, and their absence, on drug withdrawal, precipitates depression. The psychostimulants are therefore particularly desirable for those suffering retarded depression, although less so for those suffering agitated depression.

Sustained amphetamine psychosis lasting days to weeks has been described in individuals with no apparent premorbid major mental illness who develop this psychosis whilst taking the drug and in whom the psychosis persists for weeks after the drug is discontinued. The original report of the phenomenon (Young & Schoville, 1938) was of a case where the psychosis persisted for over a year. In contrast, cocaine commonly induces a rather similar psychosis—resembling acute paranoid schizophrenia—but this is much less protracted after drug discontinuation. Usually the symptoms dissipate after the "crash phase" of the withdrawal. In a study by Satel *et al.* (1991) of one hundred cocaine-dependent males, none reported cocaine paranoia extending beyond the crash phase. Conversely, in a series of 66 cocaine-using schizophrenic and bipolar patients admitted for disorganized behavior, all remained psychotic for at least 42 days. Furthermore, their psychotic symptoms required significantly higher neuroleptic doses to treat than had been the case prior to their cocaine abuse—that is, cocaine exacerbated their underlying psychotic disorder and induced psychotic decompensation

Another study on "psychosis proneness" to cocaine intoxication (Satel & Edell, 1991) found that individuals with a 'proneness' to cocaine psychosis can be identified in several ways. These neurobiologically vulnerable individuals had elevated scores on the Perceptual Aberration Scale and the Magical Ideation Scale—two measures of abnormal thinking. Most importantly, they found that users who experience acute transient paranoia when using cocaine were most likely to become chronically psychotic on protracted cocaine abuse.

Although chronic abuse of amphetamine more regularly induces a paranoid schizophreniform (schizophrenia-like) psychosis than does abuse of the shorter-acting cocaine, some individuals are uniquely and "abnormally" vulnerable, predisposed, to amphetamine psychosis. Those with paranoid and psychotic disorders are obviously vulnerable, but high-functioning borderlines can readily be decompensated and their kindled (Post & Kopanda, 1976) or heightened vulnerability to subsequent psychosis is believed to be long-lasting (Graff, Baer & Comstock, 1977; Tomiyama, 1990). Nevertheless, cases have been reported (Gold & Bowers, 1978) where no obvious predisposing psychopathology could be found

Organic Hallucinogen-Induced Psychoses

There are many varieties and pharmacological families of hallucinogens, differing from each other mechanistically and in other ways, a complete exposition of which lies outside the scope of the present chapter. To further complicate our understanding, the effects of the hallucinogens, both desirable and undesirable, are exquisitely sensitive to the setting of their use, and acute adverse effects can easily result if the environment in which the drug user finds himself

turns threatening or dangerous. A general appreciation of the acute and chronic pharmacodynamic effects of these drugs on reality testing in particular can be obtained by comparing and contrasting two prototypical agents from different pharmacological classes: LSD and PCP.

LSD

It must be mentioned at the outset that although the *visual hallucinations* or *synaesthesias* (the overflow of one sense into another) that are induced by LSD are the most well-known effects of the LSD 'trip,' not everyone experiences these to the same degree and in some cases (particularly in regular users in whom tolerance to this effect develops early) they do not experience them at all. LSD nevertheless exerts subjectively desirable effects even when it does not produce frank visual hallucinogenic entertainments, although these effects can be difficult to describe. The drug is activating and stimulating, it induces a subjective sense of 'connectedness' that may be grandiose, joyful and divine. It enhances the sensation that the religious refers to as 'epiphany,' a symptom that may also be experienced in endogenous schizophrenia.

Tolerance develops to LSD's hallucinogenic effects after a single dose, but dissipates in part after a few days. Use of the drug is thus not typically continuous, unlike marijuana or cocaine, but discontinuous, as a rule.

We can usefully divide the **adverse** effects of LSD into three phases: **early acute** reactions which accompany the acute intoxication itself, **recurrent** reactions which crop up after the drug has left the body, and **late prolonged reactions**.

The *early acute* adverse reactions of LSD are *panic* and *confusion*. Panic sets in when the user becomes overwhelmed by sensations, usually of depersonalization and paranoia and of loss of control. Anxiety can become disabling. This is the phenomenon of the 'bad trip.' Confusion induced by the acute LSD reaction is often characterized by delusions of grandeur and poor judgment. The user may attempt to fly or to walk on water or to 'pass through,' ghostlike, a moving car. There is a relationship between personality style of the user and the type of acute adverse experience in response to LSD. Klee & Weintraub (1959) found that persons who were mistrustful, complaining, fearful and who relied on projection as a defense were more likely to have paranoid symptoms during the LSD experience. In a study of normal subjects given LSD experimentally, Langs and Barr (1968) found that psychotic experiences under LSD influence could be predicted from predrug Rorschach testing which revealed paranoid features and potential for thought disorder. Of particular interest is the observation that drug-induced psychotic symptoms occurred in 90% of relatives of schizophrenics, the implication being that a heavy genetic loading accounts for the neurobiological vulnerability to LSD psychosis.

The *recurrent* symptoms of LSD are of two types: *early* and *late*. The early recurrent effects reportedly occur within a short time after the drug has left the body, usually within 72 hours. They usually resemble the early acute reaction but without any synaesthesiae or hallucination. *Late onset recurrent* symptoms are the spontaneous re-occurrence of the acute LSD experience in the absence of the drug. Sometimes called 'flashbacks,' as far as we can tell, these recurrences can develop in both psychotic and non-psychotic people. For the former, it is not always possible to distinguish between symptoms of a continuous schizophrenic episode and those to which LSD use has contributed. The reappearance of the symptoms may be

either pleasurable on not, depending on the situation (the setting) of the user. Because the drug has clearly left the body at the time the recurrent reaction occurs, these represent a manifestation of an ongoing organic brain syndrome.

A word of caution should be mentioned about the subtlety of some of the prolonged LSD effects. McGlothlin's (1969) study found that even those LSD users who denied any protracted symptoms, and in whom no overall organicity could be measured neuropsychologically, nevertheless scored poorly on the category test compared with their high scores on the verbal measures. Abstract abilities are known to be more impaired by CNS damage than are verbal abilities, and the category test is the most sensitive subtest in the Halsted-Reitan battery for detecting organicity. A high verbal-low abstract score combination is a warning indicator of organic brain damage.

The prolonged reactions induced by LSD are of psychosis and of chronic anxiety. The LSD psychosis is a relatively enduring clinical condition which resembles acute schizophrenia and persists well after the drug has left the body. The extent to which pre-experience psychoticism contributes to prolonged psychotic reaction has not been precisely defined. Much of the research on this subject came from the days of legal therapeutic LSD use in the 1960s. Blum (1964) estimated a rate of 20 to 33 per 1000 persons who took the drug under medical supervision in California. Tucker's (1972) study in schizophrenic versus nonschizophrenic LSD abusers showed a clear tendency of LSD abusers regardless of diagnosis to have increased intrusions of primitive drive material (in projective tests), higher penetration scores and higher responsivity, all pathological measures of abnormal thinking style. The degree of thinking disorder was related, they found, to the length of time LSD had been abused.

The organic damage that LSD wreaks on the brain of the user is qualitatively—and mechanistically—related to the acute effects of the drug. Tolerance itself is of course an organic change. To overcome this tolerance, which as described above is short-lived if the drug is used acutely, users must space their doses apart in time or increase the dose consumed in order to achieve an equivalent effect. The drug does not cause dependence or withdrawal, however.

Hallucinations and synaesthesias occur in the visual system most prominently and persistent psychotic reactions also involve the visual system therefore. The "LSD flashback" may be precipitated by marijuana use (according to a military study) but is apparently not triggered by stress alone. The exact mechanism of flashback precipitation is not fully understood, although the phenomenon is well described. Abraham (1983) has formally studied the visual character of the LSD flashback and finds the following typical elements:

Flashes of color: unexpectedly and without apparent stimulus, often described as a sheet of lightning shooting across both visual fields.

Geometric pseudohallucination: subjects report geometric figures come and go. Since there is insight, these are pseudohallucinations. Examples include "sparkles" or visual fireworks, lattices, colored transparent doughnut-shaped images and large transparent blobs.

Geometric phosphenes: simple geometric patterns persisting with eyes closed.

Halos around objects: halos and mists about peoples' heads.

Illusions of movement: stable objects appear to wave, roll undulate or jump, usually in the periphery of vision, often at the rate of the subject's heart or respiration.

Imagistic phosphenes: phosphenes of unbidden, formed images, **not geometric** patterns, generated on closing the eyes or pressing on the eye.
Intensified colors: objects take on momentary brightness of color, **then return** to normal color.
Micropsia: the perception of an object smaller than reality
Macropsia: the perception of an object larger than it really is
Negative afterimages: an image is seen in colors complimentary to that of the primary stimulus
Positive afterimages: images seen in the same color as the stimulus
Trailing phenomena: formed, positive, often scintillating afterimages that follow the stimulus as it moves

Two other phenomena which may be present constantly rather than intermittently are **acquired color confusion** and **difficulty reading**. The chronic impairment in color vision that is characteristic of the protracted LSD effect was studied in greater detail by Abrams (1982) who concluded that it was present in LSD users both with and without flashbacks at least two years after their last drug use. Since LSD is known to exert a component of its action at the primary visual relays of the lateral geniculate bodies, these persistent visual effects most probably represent an organic derangement of the perception of color vision—a synaesthesia of color tones—rather than any defect in visual acuity or action on the eye itself.

Phencyclidine

Phencyclidine, PCP, an analogue of the veterinary anesthetic Ketamine, is a drug entirely different from any other hallucinogen. Some pharmacologists argue that these agents are in a class by themselves. Certainly PCP's principle unique effect is to induce a state of dissociation rather than hallucinosis. Once available for clinical use as an anesthetic in humans, the drug fell into disrepute because of its untoward emergence reactions and its liability for abuse. The distinction between acute and chronic effects of PCP abuse are confounded by the fact that its low lethality encourages its consumption at vast doses whose effects can last for days. Burns and Lerner (1976) record some acute episodes lasting fifteen days.

Chronic users of PCP report smoking 100 mg or more of PCP sprinkled on parsley on a daily basis for several months (Burns & Lerner, 1981). Subjective changes are experienced within five minutes of smoking, reaching a peak in 15 to 30 minutes and persisting for up to six hours. Chronic users report *"not feeling entirely normal"* for up to 48 hours after smoking PCP. The drug is described as having intense effects on thinking, mood, sense of reality and time perception. Thinking is (subjectively) speeded up, while time is (subjectively) slowed down. Mood is intensified with almost all users feeling happy, euphoric, with a feeling of strength and endurance, and *"everything is (reported as feeling) different from everyday reality."* Religious thoughts and preoccupations with themes of death are frequent. Burns and Lerner's cohort described having difficulty in *"accomplishing things"* and in having to think about moving or talking, and feeling restless and nervous. Tolerance to the subjective effect of the drug required a four or five-fold increase in the amount smoked over the first two to six weeks of use. Psychological dependence, described as a craving, was reported, but no withdrawal syndrome was noted. Acutely the drug was reported to prevent sleep and decrease appetite.

Chronically, users reported difficulty with thinking and problems of recent memory and speech during and for several months following long periods of regular use.

Chronic use of PCP engenders changes in the personality of which the user has ongoing awareness. Fauman and Fauman (1981) studied a cohort of 25 PCP abusers and reported that 32% reported their mood to be more angry with time, more irritable and more violent. Fifty-six percent described feeling paranoid, antisocial, depressed, lonely and isolated from people. Sixtteen percent on the other hand reported no chronic adverse experiences. In an earlier study of a cohort of sixteen chronic abusers, Fauman and Fauman (1979) reported that nine described PCP as their favorite drug and 10 reported regularly injecting it. Twelve of the 16 subjects committed violent acts. Some relationship was found between violence and other historic set variables. There was no relationship between violence and having been beaten as a child. There was however a relationship between PCP associated violence and prior arrests for assault. Ten of the 12 violent PCP abusers reported 20 separate violent acts, seven without weapons and thirteen with a knife, these latter attacks being directed at strangers. Two subjects reported bizarre self-destructive acts. One such act involved the subject branding himself with a crucifix on the chest, another was found with multiple self-inflicted facial lacerations lying in a pool of his own blood and a third tried to jump from an attic window. The only clear predictor of PCP associated violence seems to be a prior history of violence. Fauman and Fauman (1981) forensically classify PCP associated violence into four typologies:

Type I	Reality oriented, goal directed, coherent thought process, memory and impulse control intact, violence is often related to drug dealing.
Type II	Unexpected, impulsive acts, diminished capacity caused by the drug, confusion present but memory of the act is intact.
Type III	Bizarre or idiosyncratic violence, diminished capacity retaining complex actions, possible stereotyped, sadistic murder or self-mutilation, often no memory of the event.
Type IV	Disorganized, psychotic, organic agitation. Chaotic, uncoordinated violent behavior.

The PCP psychosis is schizophreniform and characterized by violent and aggressive behavior, paranoia, delusions and auditory hallucinations. The psychosis is unresponsive to neuroleptics (to antipsychotic drugs) and persists for four weeks or more (Burns & Lerner, 1981). Twenty-five percent of PCP psychotics have a preschizophrenic behavioral history and subsequently, in the absence of the drug, develop a more classical acute schizophrenic psychosis which is neuroleptic responsive. Seventy-five percent of chronic PCP psychosis cases have no prior history of behavioral or psychiatric problems. Return to the use of PCP following initial recovery again leads to a psychotic episode.

Nearly all cases of PCP psychosis are associated with chronic use, not acute use. The psychotogenic effects of PCP are thought to be in some way related to the endogenous processes of schizophrenia and—as described above—chronic schizophrenic patients are particularly susceptible to psychotic exacerbation on chronic use. In studying the acute PCP exacerbation, one group of four such schizophrenic patients given a single, small, dose of PCP took

four to six weeks to recover. They are the exception, however, and in a cohort of 102 schizophrenics acutely administered PCP, only 5.9% suffered exacerbation (Luby *et al.*, 1959). On the other hand, in a series of 1243 nonpsychiatric cases administered PCP for surgical anesthesia, the incidence of psychosis was reported as zero.

Conclusions

This chapter has surveyed only a fraction of the multiple factors influencing interindividual drug response, and has by necessity of brevity ignored many of the common determinants of drug effect, such as medical illness, drug interaction, drug withdrawal syndromes, diet and obesity. An attempt has been made, however, to show that pharmacology is vastly more complex than the general public is aware of and each and every case of drug administration has the potential to differ markedly from the "average" response. Multiple factors influence this variation from the norm, and have their biological basis in the unique history and physiology of the user or patient. Effects which are "rare" in the general population as a whole tend to be concentrated in the forensic arena, where adverse experiences are preselected for attention by the behavior or toxicity of the user's response to drug use. The Disability Examiner in the forensic field is thus certain to be confronted by a greater proportion of cases of neuropharmacologically adverse effects of outwardly unusual or mysterious etiology than other practitioners.

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