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TRANQUILIZER

Addiction, dependence, withdrawal syndromes, memory disturbances, amnesia, disinhibited behavior, violence, impulsivity, automatistic and somnambulistic states, and cognitive and neuropsychological impairments result at least in part from activation of receptors in the brain for the neurotransmitter Gama Aminobutyric Acid (GABA)

This mechanism is responsible for many of the common, shared, and similar actions of various tranquillizing drugs used for relief of anxiety, for night-time sedation, as anticonvulsants, as a muscle-relaxant, and for surgical anesthetic purposes. These tranquillizing drugs of superficially very different chemical classes share this GABA mechanism, and they produce effects similar to beverage alcohol, ethanol.

These drug effects, alone and in interaction with other drugs, combine with idiosyncratic neurobiological vulnerabilities to bring the user's behavior to forensic notice in a wide variety of criminal and civil cases.

The recent death of singer Michael Jackson has focused popular attention on the drug propofol (Diprivan) that is relatively unknown outside of hospital anesthesiology. This drug shares many pharmacological similarities with a number of tranquilizing drugs that are widespread and common in use and abuse and form the bulk of the pharmaceutical money train. The relative availability and prevalence of illicit (non-prescribed) or non-medical use of tranquilizing drugs has paralleled their emergence into medical markets and constitutes a major problem in drug abuse. This review addresses a common mechanism, and certain common effects, shared by the majority of currently-available tranquilizing drugs of widely different chemical families' action

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at the brain's $GABA_A$ receptors (described more fully below). Notwithstanding these mechanistic similarities or commonalities, however, different members of the class also exert actions at non-$GABA_A$ sites and mechanisms in addition.

The purpose of this article is to provide an understanding and appreciation of the shared and common $GABA_A$ mechanisms and effects that tranquilizing drugs mediate on brain, mind, and behavior in circumstances of forensic relevance. Although the incidence rate of disabling psychotoxic effects caused by $GABA_A$ stimulation is relatively rare in the general population of therapeutically-prescribed users, it is higher in the drug abuser population, and in both populations of users and abusers, the criminal and civil justice systems act as a sieve to select and concentrate these cases of forensic interest.

Tranquilizing drugs are used for a variety of medical purposes: relief of muscle spasm (spasmolytics), anxiety relief, treatment of panic attacks (anxiolytics), epi-

lepsy treatment (anticonvulsants), nighttime insomnia relief (hypnotics), conscious surgical sedation (sedation and amnesia), and complete surgical anesthesia (unconsciousness, insensibility). Given in deliberate overdose, they are used for pest control and animal euthanasia and—in the United States—for prisoner execution, either as a component of a serial drug mixture, or, as recently adopted by the state of Ohio and perhaps in other states to come, as a single drug injection (thiopentone). In many cases, the same drug is used for more than one such intended purpose and most of these tranquilizing drugs—at least in a portion of their pharmacological spectrum—have in common a shared or closely related mechanism of action at the receptors on nerve cells in the brain and spinal cord for the neurotransmitter GABA. Therefore, regardless of the tranquilizing drugs' structural class (barbiturate or carbamate or benzodiazepine or imidazopyridine etc.), they all, to some extent and in part, act in the brain to facilitate the ac-

tion of GABA at the "Type A" GABA receptor (the $GABA_A$ receptor). They share this mechanism with ethanol, also known as beverage alcohol.

Like beverage alcohol, the acute effects of tranquilizing drugs may be forensically relevant in criminal and civil law cases involving driving or operating machinery or other intoxicated, dis-coordinated or disinhibited or impulsive behavior or misbehavior or in poisoning, homicide or suicide issues. When chronically used (repeatedly taken over time) other complex forensic neuropharmacological issues emerge, including dependence and withdrawal states resulting from changes in brain biochemistry caused by repeated use of the tranquilizer. In addition, the adaptive changes wrought by these drugs in the brain over time and their interactions with other drugs taken or co-administered typically need to be accounted for and understood in neuro-behavioral terms (see below) in order to evaluate their forensic relevance.
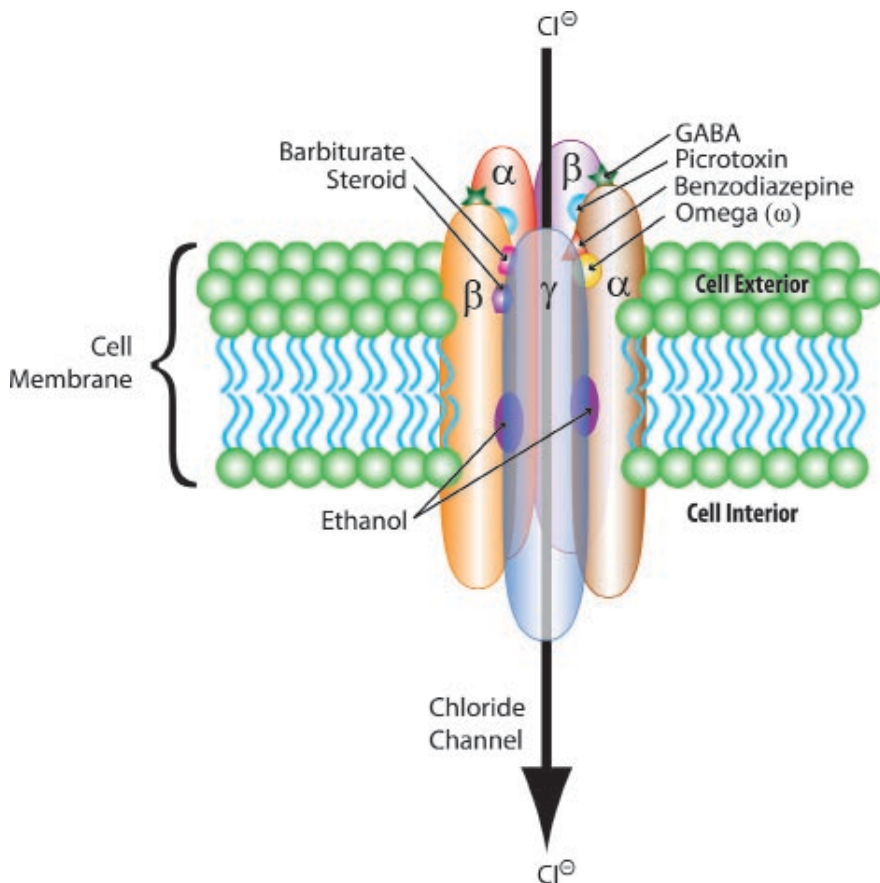
Figure 1

Schematic representation of the GABA$_A$ receptor complex comprised of α, β and γ, subunits forming the chloride ion pore, spanning the nerve cell membrane. Flow of chloride ion (Cl⁻) is from outside to inside the cell when GABA binds to its receptor. Receptors are schematically shown for steroid, barbiturate, benzodiazepine, ω = omega, ethanol (alcohol), picrotoxin and GABA (Gamma Aminobutyric Acid) ligands.

Tranquilizing drug effects on cognitive function can influence alleged cognitive disability as relevant to brain injury claims or compensation issues, or employment disability claims, and can interfere with performance in the neuropsychological tests used to evaluate such brain function. Under certain circumstances and in certain individuals—described more fully below —tranquilizer intoxication can influence "competence at the time of the crime" or "competence to be tried" and drug-influenced memory or the absence of this (amnesia) may enter into insanity and legal competence considerations. Where guilt is not at issue in a criminal case, the effects of these drugs may nevertheless bear upon a defendant's culpability and at sentencing may be relevant to mitigation of punishment. The issue of voluntary versus involuntary intoxication is frequently raised in forensic cases involving the intended or unintended consequences of tranquilizing drug use, either through lack of notice given to the user by the prescriber (if medical, or the perpetrator, if criminal) or because the illicit user had no understanding or an-

ticipation of the likely drug effects, and in either case drug interactions may be paramount in an interpretation and understanding of consequences on the mind, brain and behavior of the consumer.

Shared mechanisms of different tranquilizer types: the GABA$_A$ receptor complex

Gamma Aminobutyric Acid (GABA) is the most abundant neurotransmitter in the central nervous system, and GABA receptors are widely distributed throughout the brain, with high concentrations in the cortex and limbic system. There are two types of GABA receptor ("A" and "B") of which the B-type is a metabotropic G-protein coupled complex and the "A" type (GABA$_A$) is a ligand-gated chloride ionophore, a chloride ion channel spanning the thickness of the nerve membrane, which channel pumps chloride ion into the nerve-cell upon stimulation by GABA.

The chloride ionophores on which GABA$_A$ receptors occur are a family of related complexes composed of several types of subunits (called alpha, beta, gamma, del-

ta and rho, α, β, γ, δ and ρ subunits) surrounding a central pore or channel in the nerve membrane through which chloride ions pass (Levitan et al 1988, cited in Crews (2004)[1]. In different parts of the brain, and on different nerves, different assemblies of these subunits allow a wide variety of different types of GABA$_A$ receptor-linked ionophores to be formed by varying the type and number of subunits. The receptor complex spans the postsynaptic membrane as illustrated schematically in **Fig 1**, and receptors—neurotransmitter recognition patches for various chemicals or ligands— are formed either on the subunits, or where subunits meet or within the chloride pore itself. In this article, the chloride pore assembly responsive to GABA or drug stimulation is referred to as the "GABA$_A$ receptor complex."

In contrast to the barbiturates, benzodiazepines cannot directly open the chloride channel, but they facilitate GABA's ability to do so. Chloride influx at the GABA$_A$ receptor complex hyperpolarizes the cell membrane, making it more negatively charged on the interior relative to the exterior, which renders it less likely to conduct an action potential, and thus the effect of any ligand binding (GABA or ethanol or drug) is inhibitory on the nerve.

Common mechanisms, cross-tolerance

The different types of sedative tranquilizers discussed here each exert a similar facilitatory effect on the GABA$_A$ receptor complex, but when the tranquilizers are used in combination, their interaction is multiplicative (either additive or potentiated, synergistic, see below for discussion). It follows, too, from their shared and common site of action that there is functional cross-tolerance between these different drugs. Thus a withdrawal syndrome resulting from discontinuation of ethanol (beverage alcohol) in a dependent alcoholic ("*delirium tremens*") can be arrested by administering a benzodiazepine such as diazepam or alprazolam or lorazepam. Although not recommended, the reverse is probably true as well: alcohol suppressing the withdrawal syndrome resulting from chronic benzodiazepine discontinuation.

Problems of use and abuse

The different families of sedative drugs that act as agonist facilitators, or stimulators, of GABA transmission at the GABA$_A$ receptor
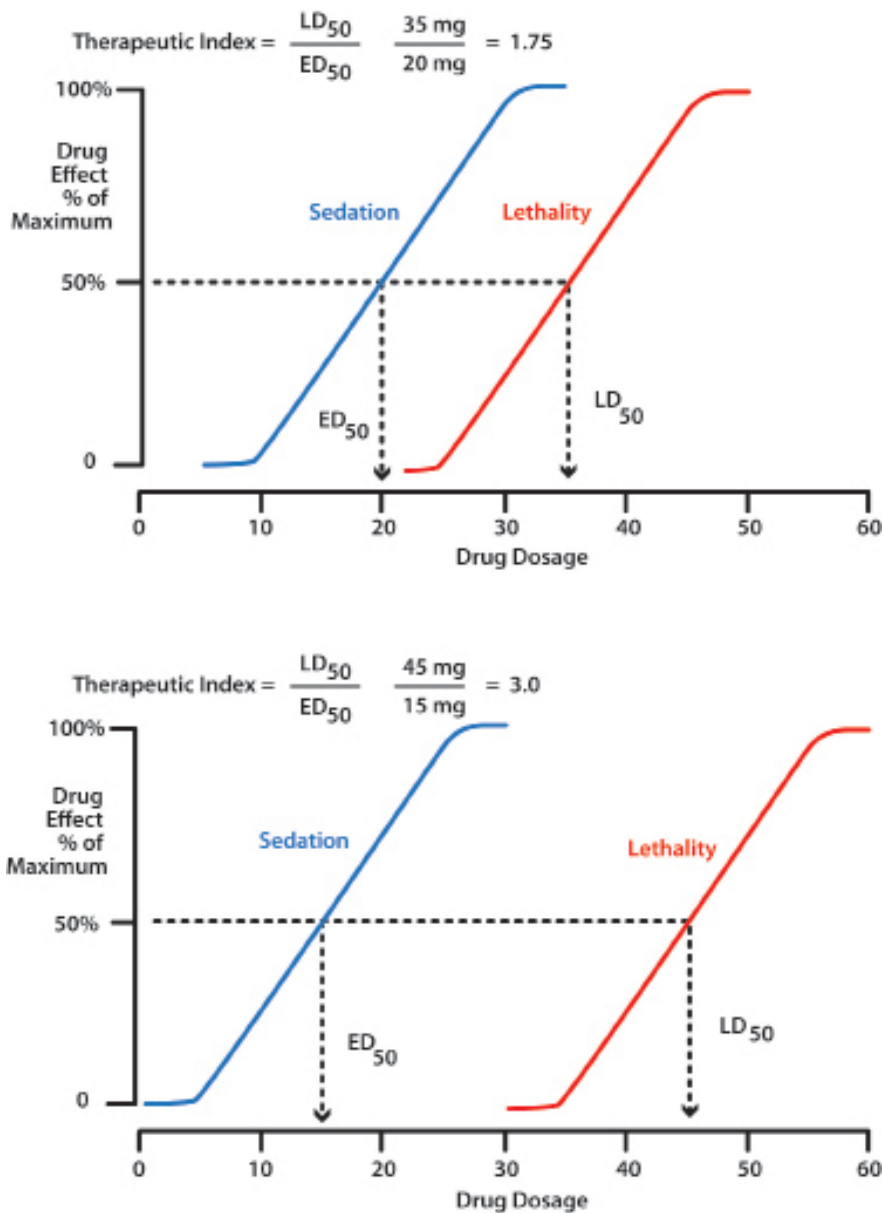
Figure 2
Schematic illustrating the concept of "therapeutic index" for sedative drugs. Upper graph shows the dose-effect curves for a drug whose death or lethality curve overlaps with the dose-range of the drug's sedative effect range. ED50 = Effective (sedative) Dose for 50% of the population treated, LD50 = Lethal Dose for 50% of the population treated. The therapeutic index is small. Lower graph illustrates the case for a drug where sedative and lethal dose effect ranges do not overlap. The therapeutic index is larger.

complex include barbiturates, carbamates, some anesthetics and steroids, all benzodiazepines, and the now proliferating 'Z' drugs such as zolpidem (Ambien) and its relatives, including zopiclone. $GABA_A$ stimulating drugs have been both used and abused for many years, and the intended and unintended effects often produce disinhibited and impulsive behavior that exceeds socially acceptable bounds, such as memory impairment; outright amnestic states that confound criminal investigation, prosecution and defense; automatisms and somnambulistic ("sleepwalking") states; chemical submission; discoordinated movement and ataxic gait; and neuropsychological and cognitive impairment. **Cognitive impairment** produced by these drugs, or withdrawal from a dependent state on these drugs, may affect a person's competence and ability to testify, which becomes relevent in civil and criminal cases. In certain people and under certain circumstances, **violent rage** is provoked by these drugs. Forensic cases involving sedative tranquilizer drug effects may involve any one or more of these drug-induced dysfunctions in perpetrators, victims, or witnesses to crime or in law enforcement, judges, counsel, or court personnel. In civil cases, traquilizer drug ef-

fects may relate to competence, disability, or injury evaluation.

In the majority of forensic cases involving sedative tranquilizers, including death due to overdose, the drug is combined and interacting with another drug. Popular illicit combinations include beverage alcohol, stimulants (called "speedballing"), and opiates (called "boosting", see below for discussion).

Forensic cases involving sedative tranquilizer use (licit) and abuse (illicit) are found throughout the entire spectrum of drug interactions and criminal misbehaviors. Though their acute use is behaviorally and psychoactively intoxicating, a host of different problems confound their chronic use including sustained memory dysfunction and other cognitive impairments, exacerbation of depressed mood, tolerance, dependence, and withdrawal states on discontinuation of the drug.

History and prevalence of the $GABA_A$ agonist drugs:
Current problems of forensic concern caused by tranquilizing drug action are merely the leading edge of an historical wave. In seeking to understand the present context and future direction of this wave it helps to have an historical understanding of the evolution, use, and abuse of these drugs.

The 1966 novel *Valley of the Dolls* by Jacqueline Susanne, later made into a film, depicts the recreational, and later compulsive, use of tranquilizing drugs (the "dolls") by three young women, who combined these drugs with stimulants .

The "dolls" of the story were barbiturates, Seconal and Nembutal, and notwithstanding their calming, euphoric, and subjectively delicious effect on the anxious user, their therapeutic index (the ratio, derived in laboratory animals, of *therapeutic dose* to *toxic dose,* see **Fig 2**) is quite low. The difference between effective and lethal dose is small, and their potential for causing death on overdose is very high.

Given the demonstrated market potential of tranquilization and the public thirst for anxiolytic drugs, the lethal disadvantages of the barbiturates led the pharmaceutical industry into a driven search for less-lethal alternatives and in the mid-twentieth century several functional analogues of the barbiturates were introduced: methylpyrylon (Noludar) in 1948 [2], followed by glutethimide (Doriden) in 1954, then ethylchlorvynol (Placidyl [3], to which the late

U.S. Supreme Court Justice Rehnquist was famously addicted) and meprobamate (Miltown) in 1955. Meprobamate was the first of the carbamates, having been discovered serendipitously in 1946 [4]. Though these drugs differ chemically and structurally, all are agonists at the $GABA_A$ receptor, like alcohol and barbiturates.

By 1957 more than 36 million prescriptions had been filled for meprobamate in the United States alone, a billion doses had been manufactured, and the drug accounted for fully one-third of all prescriptions written in that year [5]. It did not take long, however, before the realization dawned that addiction and dependence, with a withdrawal syndrome resembling the barbiturate on discontinuation, had followed the carbamate family into the marketplace [6].

Other than being technically describable for marketing purposes as "nonbarbiturate in structure" (a marketing ploy that which would later be used with the non-benzodiazepine, imidazopyridine z-drugs such as zolpidem, zaleplon and zopiclone, see below), the carbamate drugs and their successors acted pharmacologically in a similar way to the barbiturates at the $GABA_A$ chloride ionophore and, while markedly less lethal than the barbiturates they qualitatively presented the same spectrum of disadvantages. Pharmaceutical innovation rapidly led to the introduction of carisoprodol (Soma, which is still very popular), which is in fact both a drug and a pro-drug: active itself, the body metabolizes it, transforms it, to meprobamate, the barbiturate-like carbamate described above. Carisoprodol and meprobamate are advertised as muscle relaxants, yet they have no direct effect on muscles. Their relaxant effect, like that of barbiturates, is mediated at the brain and spinal cord.

Competing with these agents for the nighttime hypnotic (sleeping pill) market was methaqualone, another $GABA_A$ agonist drug (synthesized in 1951 and called Quaalude or Sopor in the United States and Mandrax in Britain). Its specific binding site on the $GABA_A$ receptor complex was not well defined, but the drug enhanced benzodiazepine binding, which revealed its allosteric action at the $GABA_A$ complex. Methaqualone was introduced in the United Kingdom in 1956 and to the Unied States market in 1965. It was described as a "safe non-addictive barbiturate substitute." Drug users and abusers appreciated its "sen-sual euphoric state and relaxed intimate mood," and by 1965, it was the best selling sedative in the U.K. market. By 1972 it was the sixth most popular in the U.S. market and its abuse had reached "almost epidemic" proportions (Foltz, Fentiman & Foltz, 1980)[7]. It has since been withdrawn from the US market, being placed in "Schedule 1" in 1984.

Although barbiturates continue as a mainstay of general anesthesia and for use as anticonvulsants and anti-epileptics, they and their relatives were largely supplanted for daytime tranquilizer and hypnotic use by the benzodiazepines following introduction of the first of this class, chlordiazepoxide (Librium) in 1960, which discovery emerged serendipitously from work on dyestuffs by Hoffman-LaRoche (now known as Roche) scientists in the mid-1950s. Subsequent work on the metabolite of Librium, demoxepam, led to the development of diazepam (Valium) about four years later. Valium was wildly popular, and by the mid 1970s about 8,000 tons of benzodiazepines were sold every year. Valium maintained the lead for a decade until Upjohn's 1981 introduction of alprazolam (Xanax) displaced the Roche product as the most popular.

Balkrishnan and his colleagues gathered six years of outpatient office visit data—between 1996 and 2001—from the National Ambulatory Medical Care Survey (NAMCS) and analyzed the treatment patterns of patients 18 and older who reported sleep problems. They found that nearly two-thirds of those doctor visits resulted in medication prescriptions for a person's sleep difficulties, and three-quarters of those prescriptions were for a benzodiazepine. (Five of the 13 kinds of benzodiazepines on the market in the United States are indicated for treating insomnia) [8].

According to the BioVenturist database, a pharmaceutical industry research tool, worldwide sales of alprazolam, a drug which went generic in 1993, were US$409 million in 2005, US$316 million in 2006 and US$325 million in 2007. According to IMS Health Data, a pharmaceutical marketing intelligence agency, annual sales of alprazolam ER tablets (the "extended release" form) in the United States were approximately $53.9 million for the 12 months ending December 2006 [9]. As with earlier generations of sedative tranquilizers, illicit use has paralleled licit use: In this same year, 2006, as reported by the National Forensic

Laboratory Information System [10], state and local drug laboratories analyzed 24,057 alprazolam, 6,360 clonazepam, 5,886 diazepam, 1,444 lorazepam, and 333 temazepam exhibits. These exhibits, of course, are but a very small fraction of the number of doses actually seized by law enforcement.

Z-drugs such as zolpidem (the tartrate salt of which is trade-named Ambien in the United States and Stilnox or Stilnoct elsewhere) is one of several structurally imidazopyridine $GABA_A$ agonist drugs to be recently introduced. The development of this 'non-benzodiazepine' imidazopyridine family of drugs, added greatly to our understanding of the $GABA_A$ receptor complex and led to the discovery that there were three subtypes of what had been hitherto called benzodiazepine receptors on the $GABA_A$ complex, at one of which zolpidem shared agonist (stimulating) properties. Flumazenil (then known as Ro-151788), the 'specific antagonist' of benzodiazepine binding to its $GABA_A$ receptor, also antagonizes the action of z-drugs, such that they are pharmacologically, to all intents and purposes "non-benzodiazepine benzodiazepines." This nomenclatural dilemma was resolved by renaming the benzodiazepine receptors to which z-drugs bind "omega" (ω) receptors, of which z-drugs are now said to have activity at the brain's ω_1 subtype. Z-drugs such as zolpidem differ from the benzodiazepines in exerting a sedative effect at a dose much lower than their anticonvulsant effect (Depoortere 1986)[11].

Zolpidem has a very short half-life and is marketed as a hypnotic (a sleeping pill). It was the second z-drug to be introduced, debuting in 1992 after zopiclone (1989) which was not introduced to the U.S. market but was popular elsewhere. The third was zaleplon (Sonata, a pyrazolopyrimidine) and the fourth to be introduced was the S-isomer of zopiclone, called 'eszopiclone' and sold in the United States under the trade name Lunesta. A fifth, indiplon, has 10 to 15 times the binding capacity of zolpidem or zaleplon, and has not yet been commercially released at time of writing. All of these z-drugs seem to act in the same way pharmacologically at the $GABA_A$ receptor, ω subtype.

The various forensic aspects of tranquilizer intoxication

In actual practice the different concepts explained below, the range of forensically-relevant effects that $GABA_A$ drugs exert, do not occur in isolation. Thus 'automatism' invariably involves 'amnesia' and amnesia may involve confabulation and the organic brain disorder that is the intoxication itself impairs neuropsychological and cognitive function. Any or all of these may be present when the drugged individual displays disinhibited behavior, which may be violent. In this article these different facets of drug effect are addressed as separate yet related entities in order to more clearly define them, but the reader is cautioned that this distinction is artificial.

Neuropsychological impairment and kinetics

At higher doses than typically employed therapeutically in the ambulant patient, the barbiturates and benzodiazepines present a similar alcohol-like clinical picture of intoxication with sluggish movement, incoordination, difficulty in thinking, slowness of speech, faulty judgment, drowsiness, staggering gait, and shallow breathing, with unconsciousness and coma occurring at the largest doses. Death at these higher doses occurs due to respiratory depression of the brain's medullary respiratory centers or positional asphyxia or inhalation of vomitus while unconscious, or some combination of these. At lower doses the acute neuro-behavioral intoxication resulting from sedative tranquilizer drug effects can be measured by tests of neurocognitive performance, similar to the tests used by neuropsychologists to assess brain dysfunction resulting from trauma.

Benzodiazepines adversely affects memory, a fact first reported by Greenblatt & Shader (1974)[12] and later confirmed in clinical trials. The intensity of this amnestic effect varies according to route of administration, dose and pharmacokinetics (Roth et al 1984)[13]. In general, the benzodiazepines with the longest mean duration of effect have long-lasting parent molecules, active and persistent metabolites, or both. Thus chlordiazepoxide (Librium) has a half-life (t ½) of 6-27 h (average 20 hours) and diazepam (Valium) has a t ½ of 21-37 h (average 24 hours), and clorazepate (Tranxene) has a t ½ of only 2 hours, yet each of these drugs are converted, metabolized, in the liver to active $GABA_A$ stimulating compounds including nordiazepam, which has an extremely variable and protracted half-life of 31-96 hours (average about 60 hours) [see **Table 1**]. Likewise, flurazepam (Dalmane) has a half-life in blood of only 1-3 hours, but the active metabolite desalkylflurazepam has a half-life of 47-100h (average 89 hours).

In contrast to these, the short acting benzodiazepines such as alprazolam (t ½ 6-27 hours, average 12 hours), oxazepam (t ½ 4-11 hours, average 8 hours) and triazolam (t ½ 1.8-3.9 hours, average 2.5 hours) do not generate active metabolites. Of the z-drugs currently available, eszopiclone, sold as the hypnotic Lunesta, has the longest half-life of 4-9 hours. Nightly dosing of long-lived drugs inevitably leads to an accumulation of drug in the body during daytime hours and unintentional carryover of daytime effects and drug interactions may occur, for instance with alcohol consumed the day following a long-acting drug's nighttime use. This likelihood increases, of course, the earlier in the day that alcohol is consumed, and early drinking is not uncommon in alcohol abusers.

An appreciation of pharmacokinetic duration is vital to an assessment of drug influence on the neuropsychological evaluation (Stein & Strickland 1998)[14]. For patients taking chronic doses steady state concentrations in blood are reached after about four half-lives. Depending on dose schedule this can be a period as long as several weeks for a healthy young adult. Recently discontinued use also introduces considerations of neuropsychological relevance because complete drug elimination takes approximately six half-lives. Further, since discontinuation of short-acting agents produces a more precipitous drop in serum level than long-acting agents, the withdrawal syndrome and mental and cognitive disequilibrium caused by the former is more intense than the latter.

Least affected by benzodiazepine action is short-term memory storage capacity, as required for digit recall, and procedural memory (recollection of previously-learned actions, such as how to drive a car). While information learned prior to drug use is retrievable, recollection of information learned under drug influence is impaired (see underline amnesia below). Most importantly: sedative effects do not predict amnestic effects, which occur with or without sedation.

Midazolam (Versed), in many ways a typical $GABA_A$ agonist benzodiazepine, is used for intravenous sedation prior to surgery. Anesthesiologists, surgeons and dentists are well aware that perioperative recall of information is reduced or obliterated in patients who have undergone midazolam sedation. The amnestic effect also occurs

Table 1
Drugs referred to in this article (in alphabetic order) showing their chemical class, their GABAA activity and their marketed purposes. Note that all benzodiazepines (=Benzo) exert muscle relaxant, anxiolytic, sedative and anticonvulsant effects regardless of marketed purpose. Abbreviations used: Barb = barbiturate, Metab = metabolite, Dep = dependant, Half-lives taken from Baselt (2008)[69]

| Generic Name	Trade Name	GABA$_A$ activity	t ½ Half-life (hours)	CLASS	Marketed Purpose				
					Muscle relaxant	hypnotic	anxiolytic	Anti-convulsant	Surgical
Alprazolam	Xanax	Yes	6-27	Benzo		•	•		
Alphaxolone	Althesin (mixture)	Yes	6-8 min	Neurosteroid		•			•
Alphadolone	(mixture)	Yes	30min	Neurosteroid		•			•
Amylobarbitone	Amobarbitone	Yes	15-40 (dose dep)	Barb		•			•
Buprenorphine	Subutex	No	18-49 (sublingual)	Opiate					
Carisoprodol	Soma	Yes	0.9-2.4	Carbamate	•				
Chloral hydrate	alphachlor	Yes	4min (10h trichloroethanol))			•			
Chlordiazepoxide	Librium	Yes	6-27	Benzo			•		
Clonazepam	Klonopin	Yes	19-60	Benzo			•	•	
Clorazepate	Tranxene	Yes	2h(metab 31-97h)						
Dexamphetamine	amphetamine	No	7-34 (urine pH)	stimulant					
Diazepam	Valium	Yes	21-37	Benzo	•		•	•	•
Eszopiclone	Lunesta	Yes (ω)	4 - 9	z-drug		•			
Ethchlorvynol	Placidyl	Yes	16-32	Carbinol		•			
Fentanyl	Duragesic	No	3-12	Opiate					
Flumazenil	Anexate	Yes	0.7-1.3	Benzo Antagonist	Overdose rescue				
Flunitrazepam	Rohypnol	Yes	9-25	Benzo		•			
Flurazepam	Dalmane	Yes	1-3 (47-100 metabolite)	Benzo		•			
Indiplon	(not yet named)	Yes (ω)	1.5-2.0	z-drug		•			
Lorazepam	Ativan	Yes	9-16	Benzo		•	•		
Meprobamate	Miltown	Yes	6-17	Carbamate	•		•		
Methadone	Methadose	No	15-55	Opiate					
Methaqualone	Quaalude	Yes	20-60	Quinazolinone		•			
Methylprylon	Noludar	Yes	7-11	Piperinedione		•			
Midazolam	Versed	Yes	1-4	Benzo		•	•		•
Oxazepam	Serax	Yes	4-11	Benzo			•		
Pentobarbital	Nembutal	Yes	15-48	Barb		•			
Propofol	Diprivan	Yes	1.5-2.5	diisopropylphenol		•			•
Ramelteon	Rozerem	No	0.5-2.4	Melatonin-mimetic		•			
Secobarbital	Seconal	Yes	22-29	Barb		•	•	•	•
Temazepam	Restoril	Yes	3-13	Benzo		•			
Thiopentone	Pentothal	Yes	6-46	Barb					•
Triazolam	Halcyon	Yes	1.8-3.9	Benzo		•		•	•
Zolpidem	Ambien	Yes (ω)	1.4-4.5	z-drug		•			
Zopiclone	Imovane	Yes (ω)	3.6 - 6.5	z-drug		•			
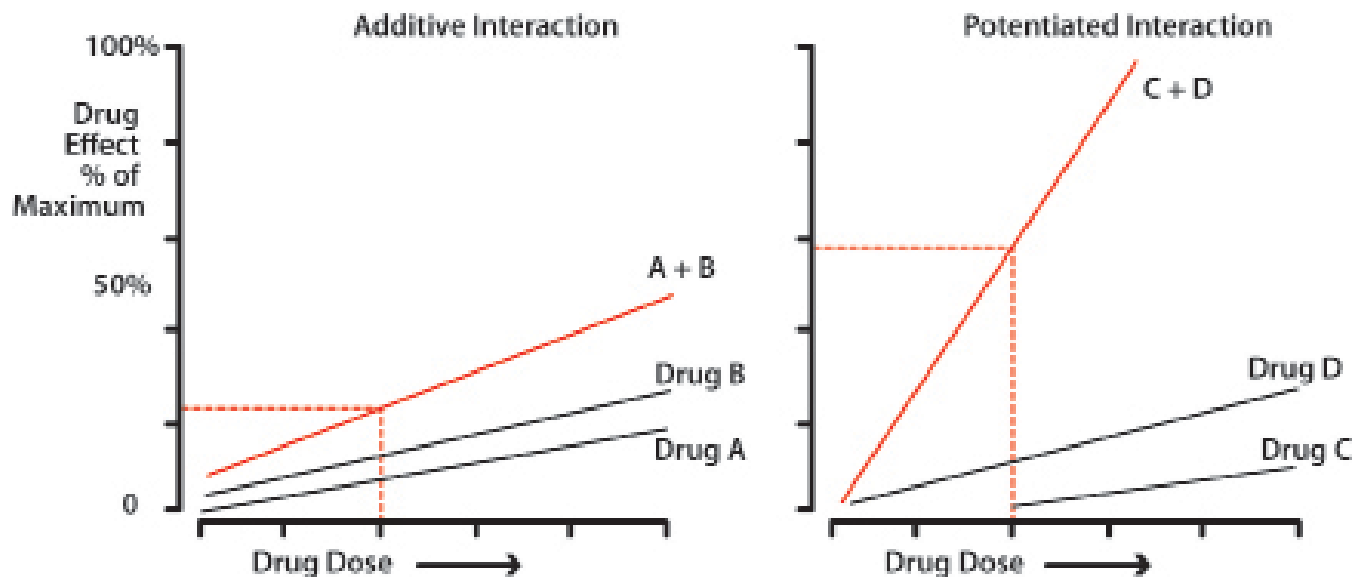
Figure 3
Multiplicative effect of drug combinations: schematic illustration of additive (left) and potentiated or synergistic (right) drug interaction. In the case of additivism; combining drugs "A" and "B" gives an effect that is the additive sum of the component drug effects. In the case of potentiation the effect of combining drugs C and D is to give a more-than-additive effect. The case is illustrated where an entirely sub-effective dose of drug C is combined with an effective dose of drug D to produce an effect vastly greater than either drug combined (dotted line).

with lower-than-surgical doses. Thompson et al (1999)[15] employed a computerized neuropsychological test battery to assess the effect of midazolam on normal volunteers administered 3mg of the drug intravenously, contrasting this with the effect of nitrous oxide ("laughing gas"). They found that both simple reaction time and choice reaction time are significantly extended by midazolam. The drug significantly impairs decision time and significantly degrades digit vigilance and impairs the ability of subjects to retain spatial information as measured by the spatial working memory test, although they found that it does not affect spatial recognition accuracy. Immediate word recall performance was severely affected by midazolam, and subjects committed significantly more word recall errors ("remembering" words that had not been presented) compared with controls. Delayed word recall performance was significantly impaired, was actually abolished by midazolam—because subjects could recall no words at all—and delayed word recognition performance was markedly impaired, as were response latencies in tests of picture recognition. They found a significant degradation of the ability of subjects to discriminate between original and newly presented stimuli.

The z-drugs of the Ambien (zolpidem) family of hypnotics – including zopiclone, eszopiclone, zolpidem etc. (see above)—

cause similar neuropsychological impairments. Wilkinson (1995)[16] investigated the effect of a 10mg dose of zolpidem (the typical hypnotic dose) and a 15mg dose on 24 normal volunteers subjected to a cognitive test battery, comparing responses to placebo. Subjects were assessed at peak time (45 minutes) and again at 130 and 230 minutes post-dose. At 45 minutes the drug degraded divided attention performance, impaired information processing rate (measured with a visual backward masking task), impaired immediate memory (measured with the Sternberg task) and degraded sustained attention measured with a vigilance task.

Clearly, a person—either perpetrator or victim or witness—under the influence of a drug acting as an agonist at the $GABA_A$ receptor could suffer memory and recall impairments that could interfere with their ability to function as a as a witness. Although likely of little practical consequence in the day-to-day life of the general population, who might forget where they parked their car, or placed their keys, such deficits may have major importance in a criminal forensic context.

Drug interactions
Alcohols: Abusers of sedative tranquilizers very commonly intentionally consume them with alcohol which markedly increases the subjective "high" of both drugs. The effect was first noted with the barbiturates in

the 1950s, and there is evidence for larger doses producing additivism of effect while the lower doses produce a potentiation or more-than-additive synergism. The distinction is illustrated schematically in **Fig 3**. Thus: while an ethanol dose of 3 mg/kg in rats has no effect on sleeping time in this species, and 30 mg/kg thiopentone (Pentothal) produces an average 24 minute sleeping time, the combination of these doses causes an average sleeping time of 217 minutes (Wiberg et al 1969, cited in Calabrese 1991)[17]. Likewise Seconal (secobarbital) at a 50 mg/kg dose in mice produces sleep lasting 11 minutes on average, and a 1.95 mg/Kg dose of ethanol produces no sleep in this species, yet the combination results in 137 minutes of sleep (Gruber 1955)[18]. Otherwise non-lethal doses of alcohol when combined with a $GABA_A$ tranquilizer can readily cause death, as separately befell musicians Janice Joplin and Jimi Hendrix, with alcohol plus barbiturate, in 1970, and the persistent vegetative state into which Carol Ann Quinlan slipped in 1976 followed a diazepam-alcohol interaction. She died of pneumonia nine years later without regaining consciousness.

At sub-lethal doses the interactive effect of $GABA_A$ tranquilizers and alcohol is largely additive in man when measured using performance tests at post-peak blood concentrations. Linnoila et al (1990)[19] tested the acute effects of alprazolam (Xanax,

Jackson's last hours

According to police reports, the following drugs were administered by Dr. Conrad Murray prior to Michael Jackson's death:

June 25 All times Pacific time zone

- Approx. 1:30 a.m., 10 mg **Valium**
- Approx. 2 a.m., 2 mg of **Ativan**
- Approx. 3 a.m., 2 mg of **Versed**
- Approx. 5 a.m., another 2 mg of **Ativan**
- Approx. 7:30 a.m., 2 mg of **Versed** while oxygen saturation of blood is monitored
- Approx. 10:40 a.m., 25 mg of **Propofol**

Michael Jackson pronounced dead at 2:26 p.m.

Each of these drugs are habit-forming

Valium
Generic name: Diazepam
- A benzodiazepine
- Primarily used to treat anxiety disorders

Ativan
Generic name: Lorazepam
- A benzodiazepine
- Primarily used to treat anxiety disorders

Versed
Generic name: Midazolam
- Category: Anesthetic, sedative-hypnotic, anticonvulsant

Propofol
Marketed as: Diprivan
- Short-acting, intravenously administered hypnotic agent
- Used as anesthetic

Source: www.drugs.com, Los Angeles Police Department, CNN, MCT Photo Service
Graphic: Junie Bro-Jorgensen, Jutta Scheibe
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2mg) in the presence and absence of alcohol in normal volunteers, measuring psychomotor and cognitive performance. Ethanol was administered three hours after drug, thus avoiding the initial period of synergism or potentiation sought by abusers who typically consume the drugs together. These authors employed a continuous tracking task resembling a driving simulator, tested verbal information processing with a word-choice reaction time task and provided a verbal memory task using a list of 12 words, six of which were presented twice. The subject was to indicate their recognition of the repeated word and the word list served also to assess recognition memory and delayed recall. Blood ethanol concentration was assessed by Breathalyzer, and the study began with a blood concentration of 65 mg/dl. Measured 4 hours after drug administration (1h after ethanol) alprazolam produced a severe deficit in performance on the word tests (memory) and the effect of ethanol on this performance was to degrade it further. Immediate verbal memory was unimpaired, but at 2 hours there was a significant reduction of related word recall (free recall) and a significant reduction of

the number of words correctly recognized (recognition memory). The effect of ethanol, in this paradigm, appeared to be additive with that of the benzodiazepines.

A similar additive effect has been found when alcohol is co-administered with zolpidem (Ambien). Wilkinson (1995)[20] administered to normal volunteers a dose of ethanol calculated to produce a blood alcohol concentration of 0.08g% (80 mg/dl, the legal level of presumptive intoxication for fitness-to-drive purposes in the USA for non-commercial drivers) over 30 minutes of consumption, following this with either 10mg or 15mg of zolpidem (Ambien) or placebo. Subjects were then subjected to a neurocognitive performance battery at 45, 130, and 230 minutes post-dose. The design was fully blocked, so that the effect of drug or alcohol alone could be compared with the combination, and a placebo beverage drunk from a glass externally scented with vodka served as the alcohol control. Measured at peak zolpidem time (45 minutes) both zolpidem and alcohol degraded divided attention, and the combination was additive. On the visual backward masking task, testing for information processing

speed, both drugs impaired performance and the combination was again additive. Likewise with the vigilance task; alcohol and zolpidem produced additive impairment. Interestingly, at the final evaluation four hours after zolpidem administration, performance on all tasks was within the normal range, except for the divided attention task: thus, although the zolpidem effect had dissipated and the alcohol effect had dissipated, the combination still impaired divided attention even though sedation or drowsiness (measured by the backward masking test) was no longer present.

Stimulants: Among abusers of stimulant drugs (cocaine, amphetamines, methylphenidate) sedative tranquilizers blunt the agitation and anxiety which occurs as a side effect of stimulant action, allays to some extent the paranoia attendant on chronic use and adds a dimension of tranquility to their jaw-grinding state of hyperexcitability and tension. In this they follow the designs of the pharmaceutical companies such as SmithKline, developer of the Dexamyl (or Drinamyl) formulation that combined amylobarbitone with dexamphetamine until this was withdrawn from the market in 1981 (see below). The illicitly co-administered combination is generically called "speedballing," although that term can also be used to refer to opiate-stimulant combinations. Stimulant abusers also employ $GABA_A$ agonists to self-medicate the psychically painful 'crash' of withdrawal when their stimulant supply has dried up or they otherwise need to end a speed run, having been continuously sleepless for many days.

Although tranquilizer abuse, unlike stimulant abuse, does not as a rule itself provoke outright psychosis, the ameliorative effect of combining tranquilizers with stimulants can enable the combined user to take more of the stimulant for a longer time and to suffer more severely from chronic stimulant psychotoxicity. Such psychotoxicity can involve many of the features usually associated with the acute psychotic break of a chronic schizophreniform psychosis, with paranoia, hallucinations (auditory, visual and tactile), delusions, grandiosity and hostility born of irrational fear.

Opiates: The combined use of tranquilizers and opiate drugs is not strictly contraindicated in medical treatment and the combination of midazolam (Versed) with

an opiate such as fentanyl is common in surgery where the effect is carefully supervised and controlled. Likewise chronic pain patients are often prescribed both opiates and $GABA_A$ drugs (benzodiazepines, carbamates, barbiturates or "muscle relaxants") for an extended time without experiencing too many problems in performing activities of daily living although they do suffer neuropsychological impairments as a result (see below). The same is true of patients in opiate substitution programs equipped and staffed to handle "multiple drug" abusers. The combination is not without hazards, however, as epitomized by the 2007 death of Anna Nicole Smith, who expired under the influence of prescribed methadone and benzodiazepines. The greatest problems of forensic concern arise when tranquilizers are used intermittently or abusively in the opiate-consuming population. The combination acutely enhances the euphorically subjective "high" of the opiate experience and is particularly attractive to opiate addicts or poorly-controlled chronic pain patients. Illicit combined use is considered a major problem by opiate treatment providers in single-modality opiate (methadone or buprenorphine) substitution programs, where users may illicitly self-medicate with tranquilizers before reporting for their daily supervised opiate dose, a practice called "boosting" (Kleber, 1994) [21].

Although substitution programs perform urine testing on patients, they typically do not test blood and unrinalysis results do not indicate current intoxication. Thus behavioral intoxication involving over-sedation resulting from "boosting" can lead to traffic accidents, and overdose death due to combined respiratory depression is not uncommon. Backmund *et al* (2005)[22] studied the records of 1,685 patients admitted for opiate detoxification, finding that daily intake of benzodiazepines was reported in 44.4% of the patients. Patients treated with methadone or codeine medications reported daily intake of benzodiazepines significantly more often than the heroin-dependent patients.

Forensic consequences of combined use may relate to malpractice claims when the drugs are prescribed unsupervised or in error and to civil liability issues when a traffic accident or death or injury occurs, and third-party claims may be involved.

In neuropsychological terms, the memory deficits caused by the $GABA_A$ stimulating drugs are magnified by opiate co-admin-

istration. Rapeli et al (2009)[23] followed a group of anxiolytic-prescribed patients who were also enrolled in an opiate substitution program. Thirteen took daily methadone and 15 daily buprenorphine as opiate substitution. The $GABA_A$ drugs used by the group included alprazolam, clonazepam, diazepam, oxazepam, midazolam, temazepam, zopiclone and zolpidem. The authors studied these patients initially upon enrollment into the opioid substitution program and again between 6-9 months after admission. Patient groups were compared with a parallel group of non-drugged normal subjects tested at the same time intervals. Rapeli et al found that Working Memory (the short-term store that maintains information that is lost without repetition), tested with the Letter-Number Sequencing task from the Wechsler Memory Scale III, was markedly impaired in patients compared with normal controls. This deficit was persistent across 6-9 months of constant drug dosing, and no tolerance was shown to the effect. List-learning was more impaired in the buprenorphine-treated group, and this confirmed an earlier finding by Lintzeris et al: that buprenorphine combined with diazepam impairs delayed verbal memory more than buprenorphine given alone (Lintzeris, Mitchell, Bond et al, 2006)[24].

Addiction and dependence

Dependence: The tranquil relief of anxiety that $GABA_A$ drugs induce is dependence-forming, in the sense that tolerance develops to their effects when used chronically, and changes in the brain which underlie this tolerance reflect a readjustment of the homeostatic balance of brain chemistry counter to the action of the drug. Once adapted to the drug's effect, the brain of the user undergoes a withdrawal syndrome in the absence of the drug, and it is this condition from which the withdrawal state is precipitated that is called "dependence." The withdrawal syndrome takes the form of symptoms opposite to the drug effect. Whereas $GABA_A$ stimulation is tranquilizing, peaceful and soporific the withdrawal syndrome is anxious, agitated and insomniac. The development of early-morning awakening that occurs after triazolam (a benzodiazepine) is used for two weeks as a bed-time hypnotic is an example of the effect of tolerance. Once this change has occurred and the brain has adapted to the drug's presence, abstinence from use causes insomnia. As barbiturates, benzodiazepines

and alcohol are also anticonvulsant (anti-epileptic) in their effects, withdrawal from a dependence on these drugs can precipitate a seizure state, and this can be provoked even in individuals who did not suffer from epilepsy before tranquilizer use.

The withdrawal symptoms that occur on discontinuation have "rebound" intensity, greater than existed before tolerance to the drug had developed. Thus anxiety treated with benzodiazepines is more intense after drug withdrawal than it was before treatment began, and panic attacks (discrete periods of intense fear and discomfort) can be precipitated by abstinence (Bashir & Schwartz, 2002)[14].

Addiction: The word "addiction" has undergone some linguistic contortions in recent years. Current medical policy in the pain management field is to avoid using the word to describe the craving a patient feels for a legally prescribed drug and to use the term "pseudo-addiction" instead (Weissman and Haddox 1993[26], Fishbain 2003[27]), reserving the word "addiction" to characterize the dependence state and resulting behaviors of the illicit (non-medical, non-prescribed) drug user. Pharmacologically this is probably a distinction without a difference. Behaviorally, however, addiction (as opposed to dependence) is usually manifest as a lack of self-control over dose escalation despite adverse consequences. The term "pseudoaddiction" as applied to opioid-treated pain patients taking more drug than prescribed in pursuit of adequate pain relief is now the preferred term adopted by the International Association for the Study of Pain (IASP 1993)[28]. Since there is rarely any medical need to prescribe beverage alcohol, the term is unlikely to gain currency in the alcohol addiction field.

In a protocol for which it would be impossible to get Institutional Review Board approval nowadays; a study performed in normal volunteers in 1958 gave the $GABA_A$ drug meprobamate several times daily for 40 days before the drug was then abruptly withdrawn. The subjects suffered insomnia, vomiting, tremor, muscle twitching, overt anxiety and some of these subjects suffered convulsions 36 to 48 hours after discontinuation (Hazilip & Ewing 1958)[29]. These signs and symptoms are facets of, and common to, the alcohol withdrawal syndrome or *"delirium tremens"* and the commonality lies mechanistically at the $GABA_A$ receptor complex.

Feeding the nation's pill habit

South Florida pill mills are the supply pipeline for users and dealers in several Eastern states. A recent sampler:
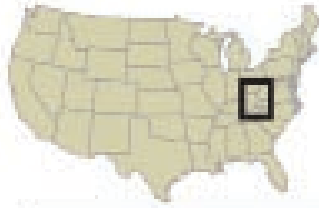
Lawrence Co., Ohio
March 23 A grand jury indicts 12 people after an undercover investigation reveals a network trafficking prescription drugs bought in South Florida

Huntington, W.Va.
March 26 Police arrest a Tennessee couple with hundreds of prescription pills worth an estimated $20,000, police say the couple obtained the pills with prescriptions filled in Fort Lauderdale and St. Petersburg

Lewis Co., Ky.
Feb. 11 Sheriff's deputies arrest four people carrying nearly 1,000 painkillers and other pills prescribed a day earlier by doctors at Fort Lauderdale pain clinics

Unicoi Co., Tenn.
Feb. 21 Four men are arrested after trying to obtain pills with prescriptions obtained from a Fort Lauderdale doctor a day earlier

Graphic: Miami Herald

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The anxiety, craving, panic, and desperation that the dependent sedative/tranquilizer abuser suffers can drive them to breach laws and conventions to maintain their supply, either by theft or deception. Such individuals can easily find themselves outside the law and subject to forensic evaluation.

Amnesia and automatism

Generally speaking, amnesia is never a defense to a crime, yet automatism may be a complete defense, and the forensic challenges presented by investigation of a case in which the defendant or victim has no memory of the offense can be quite formidable.

Resulting from an action on the hippocampus, where short-term memory is consolidated into long-term storage, $GABA_A$ agonist drugs prevent this consolidation. Memories are not later retrievable, because they were never transferred from short-term to long-term storage. The amnesia is *anterograde*, proceeding forward in time from the intoxication, and in this it differs from the *retrograde* amnesia of brain concussion. The "alcoholic blackout" phenomenon is an example of $GABA_A$ agonist anterograde amnesia. Amnesia can either be an unfortunate and problematic side effect of treatment or drug use or abuse, or it can be intentional, as for instance when the benzodiazepine midazolam (Versed, mentioned above) is medically used to produce tranquility and amnesia in patients undergoing surgery. The last thing the patient recalls on awakening in the recovery room is having received their midazolam injection in the preoperative suite. Under the drug's influence the patient does not en-

tirely lose consciousness, appears tranquil, intoxicated, often talkative prior to receiving their later anesthesia, yet none of this is later recalled as a result of anterograde amnesia. To proceed with surgery actual loss of consciousness is required, often induced by intravenous propofol, a non-benzodiazepine anesthetic agent also acting at the $GABA_A$ receptor. This is a white-colored, milky, oil emulsion that is sometimes jokingly described by anesthesia staff as "milk of amnesia" which, as earlier mentioned, recently achieved notoriety in the death of singer Michael Jackson (Mundy 2009)[30]. Flunitrazepam (Rohypnol), the aforementioned benzodiazepine often abused by youth for its drunken alcohol-like intoxicating effect, is likewise known on the street as "mind eraser" and "forget pills'"(Daderman & Lidberg 1999)[31]. Although the 10mg dose of zolpidem is typically used for nighttime sedation, larger doses have been employed as pre-operative tranquilization. In one such study comparing 20mg of oral zolpidem with 15 mg of IV midazolam, zolpidem produced significant anterograde amnesia from 30-60 minutes after administration in 45% of patients, nearly the same percentage as those given 15mg of midazolam (Pahud et al 1988)[32].

The anterograde amnesia phenomenon has been well studied in the laboratory, and in regular users of the drug is most well associated with rising blood levels in the period following dose administration. An early reported study (Kumar et al 1987)[33] gave either alprazolam 0.5mg or lorazepam 1 mg to normal volunteers three times daily. On the sixth day they were tested using a 16-word-list in an immediate and a delayed recall paradigm before and 2 hours after dosing. On this repeated dosing schedule no deficit was found in immediate recall pre-drug (when blood levels were lowest) but there was impairment of delayed recall for the list learned 2 hours after dosing (when blood levels were highest). No deficit was found in the recall of already-learned material.

Amnesia resulting from $GABA_A$ agonism leaves the subject with a memory blank that is discovered after the drug intoxication, yet during the course of the intoxication immediate (short-term) memory is intact, and the subject may function in an automatistic state, able to walk, talk, respond and engage in often apparently complex tasks although these cannot later be recalled. The subject does not appear to be sleepwalking to an

observer (but see below) and can respond to conversation in an apparently superficially meaningful way. Numerous examples of such automatisms with residual amnesia have been published in the scientific literature, often self-reports of a scientist traveling to a professional meeting and taking the drug on their outbound international air travel to assist with jet lag: they arrive at their destination, clear customs and passport control, taxi to their hotel, attend a reception, and on awakening the next morning their last recollection was of being in the aircraft (Morris & Estes 1987)[34]. It is only through eye-witness reports that the amnestic, automatistic, episode can be reconstructed.

Although apparently genuine cases of "sleepwalking" have been reported to have been induced by z-drugs, particularly zolpidem, the majority of such nocturnal ambulatory episodes are most probably automatisms. The distinction between the two can be subtle, but in sleepwalking speech is usually incoherent and the subject is largely unresponsive to their environment, their behavior incongruous to circumstances (Harazin & Berigan 1999)[35] and this is not the case in automatisms.

Automatisms with residual amnesia usually occur when the subject has taken more of the drug than prescribed or is prudent, often inadvertently, and the interaction of the $GABA_A$ drug with alcohol has a similar effect to drug overdose through an additive or synergistic process described previously (*supra*). The phenomenon may or may not be characterized by behavioral dyscontrol (which, when it occurs, can be violent). More commonly the subject simply walks, talks and acts in an uncharacteristic manner and has no memory for the events after waking from the sleep that follows. Adverse experience reports (AERs) of the more behaviorally deranged cases abound in the scientific literature, however. An early report was of the case of "Ms. A," who while treated with alprazolam (Xanax), drank approximately three ounces of 80-proof whisky, broke into her neighbors' house an hour later, and "smashed everything in sight," destroying approximately $50,000 worth of property and inadvertently sustaining lacerations to both wrists from broken glass. Returning then to her house she fell asleep and upon wakening had no memory of the offense— only vague recollections of the sounds of breaking glass (Terrell 1988)[36]. Other pub-

lished examples of $GABA_A$ stimulated automatisms include:
"taking a bath with a raincoat on…

…going to the dentist at night, having confused 11 AM and 11 PM…

… pruning rosebushes in the middle of the night… cutting up furniture with a chainsaw" (Pompidou 2001, *infra*[41]) …

…crawling in the hallway at night, the patient told the nurse he was going to mass (Yang et al 2005)[37]

When the subject is well-known and the event occurs in public, the popular press is involved. This was the case in March 2003 when Peter Buck, the then-45-year-old guitarist for the musical band REM, went on trial after being charged in April 2003 with a string of bizarre and out-of-character incidents attributed to him while flying the 10-hour trip from Seattle to London, Heathrow (BBC 2003)[38]. He pled not guilty to one charge of being drunk on the aircraft, two counts of common assault involving head steward Mario Agius and steward Holly Ward (covering them in yogurt), and one charge of damaging British Airways crockery. The trial took place at west London's Isleworth Crown Court. Cabin staff aboard the British Airways 747 spoke of him trying to load a CD into a hostess trolley, upending it and sending a cascade of crockery and food across the floor, and then attempting to slip a knife up his sleeve as he helped clear up the mess. At another stage, it was claimed, Mr. Buck had to be pulled away from an exit door after announcing he wanted to "go home," before swearing at Captain Tom Payne when presented with a "yellow card" warning him to change his behavior or face arrest.

Mr. Buck had been flying to London to perform at the Nelson Mandela concert in Trafalgar Square. He said that he "blacked out" until he woke up in a police cell. The court was told that he did not remember allegedly upending a hostess trolley, did not remember swearing at the captain, and did not remember ripping up a "yellow card" warning him to behave or face arrest.

Mr. Buck asserted that he had taken a tablet of Ambien with a glass of wine at the beginning of the trip, and through his attorney claimed that what followed constituted a state of "non-insane automatism," which under English law is an absolute defense to

criminal culpability. He was described by friends and family at the trial as otherwise the "politest, gentlest person imaginable."

Dr. Ian Hindmarch of the University of Surrey, professor of human psychopharmacology, testified for the defense regarding 'non-insane automatism' induced by Ambien (BBC 2003)[38].

Disinhibition

The frontal lobes of the brain exert inhibitory influence on lower brain areas, and serve executive functions in decision-making, planning, prioritizing, and execution. $GABA_A$ agonist drugs, in common with beverage alcohol, reduce this inhibition. The effect can be intentionally produced, as in the prescription of $GABA_A$ agonists to reduce the anxiety component of pathological 'shyness,' or the use of alcohol as a social lubricant. Persons acting under the influence of $GABA_A$ agonism are more impulsive, more spontaneous and more likely to act without regard to consequences (see below). This was earlier noted in regard to the barbiturates (Baraclough 1976)[39] and has continued through the evolutionary and sequential introduction of other, newer, $GABA_A$ agonists. This disinhibition can be particularly problematic in individuals with pre-existing frontal lobe impairment such as frontal dementia or an attention deficit disorder, but even in persons not so afflicted the effect of $GABA_A$ agonism is often a component in impulsive crimes. The subject usually describes their behavior as being "out of character." Perpetrators under the influence of $GABA_A$ agonists may impulsively steal and victims of involuntary intoxication acting under $GABA_A$ agonist influence may impulsively and disinhibitedly have sex with relative strangers or persons they normally would not choose as sex partners. If the dose is high enough they may not later recall their "voluntary" participation (amnesia, see above)[40]. Other examples of disinhibition reported in the scientific literature include:

"very high-society Mrs. Z defecated in her bed with great satisfaction while being examined by [an eminent doctor]

… a 36-year-old man engaged, in front of a witness and without restraint, in a sexual act normally practiced alone

… after receiving a 30mg dose of diazepam a 30-year-old woman removed her clothes and

made lewd and direct propositions, in front of a witness…

… a doctor uncharacteristically swearing during a [morning] vaccination session—at midday he was under the impression he had not gone to work that morning" (Pompidou 2001)[41].

Very rarely the form of disinhibitory behavior may have qualities of mania; a paroxysmal excitement, with insomnia, racing thoughts and increased energy, and this has been reported in patients both with and without pre-existing bipolar disorder. Reported initially as a rare manic reaction to benzodiazepines (Strahan, Rosenthal, Kaswan & Winston 1985)[42], the same has occasionally been reported in persons who have taken zolpidem (Hill, Oberstar & Dunn 2004)[43].

Violent dyscontrol, hostility and rage

Rage and violent dyscontrol are a special case of GABA$_A$ agonist-induced disinhibition. The production of violent rage requires both a lack of self-restraint and the presence of a motivating anger. In certain persons and under certain circumstances GABA$_A$ agonism evokes both. Ingram and Timbury (1960)[44] first reported dangerously aggressive dyscontrol and rage under benzodiazepine influence resulting from chlordiazepoxide (Librium) use. DiMascio & Shader (1970)[45] reported the same resulting from diazepam (Valium) use and Bladin (1973)[46] reported on clorazepate provoking such hostile dyscontrol, and the phenomenon came to be recognized as a rare "rage reaction" (Gardos 1968 [47], 1980 [48]). The phenomenon was originally thought to be—and was called—"paradoxical" rage, since these drugs typically reduce, or were expected to reduce, the emotional conditions from which hostility might emerge. It early became apparent, however, that albeit rare in the general population, the reaction is not in fact "paradoxical" but is reliably produced in certain persons under certain circumstances (Hall & Zisook 1981)[49]. Pre-existing hostility level is a determinant (Covi & Lipman 1977)[50], as is a past history of poor impulse control, yet the setting of drug use is also relevant. Subjects suffering a predisposing borderline syndrome, including borderline personality disorder, are particularly vulnerable and in a study of the effectiveness of alprazolam as a treatment in borderline personality disorder, fully 58%

randomized to alprazolam experienced "paradoxical"rage reactions, compared with none given placebo (Gardner & Cowdry 1985)[51]. A Swedish study of juvenile offenders who abuse flunitrazepam (Rohypnol, or "roofies"), usually in combination with alcohol, found that impulsive violence was associated with high scores on verbal aggression and boredom susceptibility in personality tests (Daderman & Lidberg 1999)[52]. Even in individuals not psychiatrically diagnosed, however, extreme interpersonal frustration is a recognized trigger of GABA$_A$ agonist-associated hostile outbursts (Karch 1979)[53]. Neuropsychological dysfunction may also provide a constitutional vulnerability to GABA$_A$ agonist induced rage: in a study of 38 patients given clonazepam (Klonopin), eight subjects who experienced aggressive outbursts were found to have mean differences of 17.5 points between verbal IQ (VIQ) and performance IQ (PIQ) as measured by the (adult or child) Weschler Intelligence Scales. The 30 patients who did not react with rage had mean VIQ-PIQ differences of only 6.5 points (Rosenfeld et al 1987)[54]. Such a VIQ-PIQ difference is often associated with antisocial personality traits.

A history of anger management problems and of alcohol abuse may predispose the individual to belligerence under GABA$_A$ drug influence. A recovered female alcoholic given midazolam preoperatively for dental surgery became so abusive and aggressive after receiving an 18mg dose that surgery had to be aborted (Fiset et al 1992)[55]. Her belligerence continued for 24 hours and the woman afterward claimed no recollection of the events. Yet no such predisposing history was reported in the case of a similar surgical misadventure, with amnesia following, of a woman under conscious sedation with midazolam undergoing breast implant insertion. Surgeons reported that force was required to control her (Rodrigo 1991)[56].

Hostility has also been reported in control subjects and in normals under laboratory conditions. Although such laboratory studies are a far cry from the circumstances in which hostility is provoked in the "real world," they may be useful for purposes of modeling the phenomenon and for study of predispositional correlates and drug interactions relevant to the effect. Alprazolam is the benzodiazepine most often implicated in this adverse reaction (Cole & Kando 1993)[57], and certainly it is the best studied in the laboratory. The phenomenon was

early investigated using diazepam (Valium) by Cherek et al (1987)[58] who used a financial game paradigm in which subjects sat before a console having two response buttons labeled A and B. They were told that they were randomly paired with another, unseen, person in a situation described to them as one in which they could earn money ("points") by pushing button A and could influence the amount of money ("points") earned by the other individual they were paired with by subtracting money from them (punishing them) by pushing button B. They were told the other person could do the same to them. Pressing button A was in fact maintained by a fixed ratio (FR) 100 schedule of point presentation. Each point delivery ("earned") was indicated on a counter mounted next to Button A and each point was given a value of ten cents. Pressing button B ostensibly delivered point subtraction (punishment) to the other person and was defined as "aggressive"— completion of each 10 presses on button B ostensibly subtracted one point (ten cents) from the paired opponent participant and started a provocation-free interval of 125 or 500 seconds.

Unknown to the participants was that there was no "other" opponent, and point subtractions (provocations) were automatically scheduled to occur at random times throughout the session. In the absence of any aggressive action (pressing button B) on their part, subjects were scheduled to receive 40 point subtractions per session.

Thirty minutes prior to each session subjects received a gelatin capsule containing either placebo or diazepam at a dose of 2.5 mg, 5 mg, or 10 mg per 70Kg of their body weight.

Subjects completed two questionnaires: a self-inventory (Profile of Mood States, POMS) and the Buss-Durkee Hostility Questionnaire at the end of the study.

Five of the seven subjects tested had reduced aggressive responding under diazepam influence at the highest dose, one subject demonstrated no change in aggressive responding, and one subject expressed increased aggressive responding in the absence of provocation that did not occur in this subject, under placebo conditions and which was not seen in the other subjects. The Buss-Durkee Hostility score of this individual was much higher than any other subject.

Bond et al (1995)[59] investigated the phenomenon of alprazolam hostility in 23 pa-

tients with a diagnosis of panic disorder that had been treated with alprazolam or placebo for eight weeks. Using questionnaires and self-ratings, alprazolam-treated patients reported at baseline feeling less hostility after eight weeks of drug treatment. The subjects were then subjected to what they were told was a reaction-time competition against an unseen opponent in another room. The subjects wore headphones and were told to select, at the beginning of each trial, one of eight intensities of sound that would be administered to their opponent if the subject's reaction time was faster than their opponent's. They were told their opponent had similar privileges. In fact, there was no opponent: noise level was increased throughout the experiment over six trial blocks and the subject heard the noise 50% of the time within each block, regardless of reaction time, and whenever their reaction time was 20% slower than their own average. The paradigm was thus provocative of aggression using noise as a punishment that the subject could inflict on their nonexistent opponent. As measured by loudness selection patients on alprazolam behaved more aggressively in response to perceived provocation than did placebo-treated control subjects. Provocation, or perceived provocation, is thus an essential element of alprazolam-induced hostility, even in subjects who report less baseline hostility under drug influence when not provoked.

Although the proportion of individuals vulnerable to experiencing 'paradoxical rage' is likely very small in the general patient population, the criminal justice system tends to select and concentrate these individuals with attributes of _set_ that include personality disorder, hostile traits, neuropsychological impairments, impulse control disorders and other neurobiological vulnerabilities to $GABA_A$ agonism-induced rage and disinhibition of its control. The tense and punitive circumstances in which such people often find themselves, confined by demographic, institutional and legal constraints outside of their locus of control, also adds an additional environmental contributing factor of _setting_. A disastrous early experience in the 1970s with using the $GABA_A$ agonist tranquilizing drugs oxazepam (Serax) and diazepam (Valium) in an attempt to control prisoners in the Utah state prison system found that:

"the benefits derived from the administration of these drugs in prisoner control were

[…] outweighed by the frequent appearance of paradoxical rage reactions and increase in hostility and aggressive tendencies in these individuals." (Brown 1978)[60]

Chemical submission

Drugging an unwilling victim into a state of unconsciousness for the purpose of robbery or rape has a long literary and folkloric history, popularized by the 'Mickey Finn' of the 1918 Chicago restaurant poisonings, and in novels such as the 1930's _The Maltese Falcon_ and the 1941 film of the same name. This, however, is not what is meant by "chemical submission," which is the name given to a state of willing compliance, usually against the user's best interest, that $GABA_A$ agonist drugs can induce in a person, the victim or subject of this intoxication. Recent reports of chemical submission have been most particularly associated with the above-mentioned benzodiazepine flunitrazepam (Rohypnol or "Roofies") in connection with its use as a "date rape" drug when combined with alcohol, but historically the state has been associated with barbiturates or chloral hydrate, and more recently, zolpidem (Ambien). Hoffmann LaRoche, the manufacturer of Rohypnol, reformulated their tablet in 1997 with a bright blue dye (cloudy in dark colored drinks), which together with its bitter taste is said to render it detectable in most alcoholic drinks.

Since the subject/victim under $GABA_A$ agonist influence is in an altered state of consciousness their consent to sex or other intrusions on their liberty cannot be said to be entirely voluntary, yet the subject is not unconscious or asleep at the time and the purpose of the assault, if it is assault, is to induce a state of loss of self-control. Submission entails making a person act as one wishes; it is not a matter of exploiting an individual who falls into a deep sleep and remains passive and incapable of action. It follows, too, that where the state is deliberately induced in another unknowingly the subject victim is in a state of <u>involuntary</u> intoxication.

The victim in submission can be manipulated into revealing their credit card number, can be induced to walk around with their aggressor without drawing attention in public and can be convinced to sign checks, all without later recollection or only fragmentary memory for these events (Pompidou 2001, _supra_). The below-mentioned 2005 case of <u>USA v Matthew O'Connor</u>, wherein

O'Connor waived his Miranda rights and made statements to police while he was under influence of the $GABA_A$ agonist drug propofol, was most likely a case of chemical submission: in a state of organic delirium he acceded readily to police request that he incriminate himself in a crime. A similar situation pertained in the 2009 case of <u>State (Georgia) v John David Clay</u>, where the defendant was under the influence of a self-administered benzodiazepine overdose when interviewed by police. Neither O'Connor nor Clay later recalled being interviewed, they were amnestic.

The picture of a chemical submission most publicized in the popular press, that of a perpetrator surreptitiously drugging an unwilling victim, probably happens less often than is claimed or believed, since in practice drug abusers, particularly youths and young adults, intentionally abuse $GABA_A$ agonist drugs socially, often willingly consuming them with alcohol. They may have no later recollection, or understanding, of what they did under its influence.

Confabulation

In chronic abusers of $GABA_A$ drugs, as with chronic alcoholics, the user's history is often a patchwork of half-remembered facts, memory gaps and confabulations. Confabulations are not "real" memories, although to the user they feel real. They are more properly thought of as unconsciously manufactured or imagined memories that "make sense" to them, that fill the amnestic voids left by drug eradication of memory. These recollections may not comport with the evidence of consensus reality, are not true in an objective sense, yet the user relating them is not consciously lying. In the recent Alaska case of _U.S. v Lusk & O'Connor_ referred to above; the defendant O'Connor made statements to law enforcement following medical treatment, and while he was still under the influence of the $GABA_A$ agonist drug propofol in the hospital. His admissions in this state of organic delirium were bizarre; his speech slipped tangentially from one thought to another, and was delivered in a poetically rhyming cadence. Some of his admissions could be—and were—interpreted by police as incriminating, but considering the entirety of his performance, which was audiotaped, it seemed clear to this examiner, and to the U.S. magistrate judge presiding, that O'Connor was delirious, that much of his speech content was confabulatory in con-

tent, and none of it was reliable. His "confession," for which he was later amnestic, was properly suppressed.

Persistent effects beyond withdrawal

Chronic use of sedative tranquilizing drugs is the norm: an estimated past-year prevalence of use in the USA was reported in 1982 from a cross-national survey conducted in over 2,000 households as being 12.9% of the population, with 14.2% of this group taking the drug for 12 or more months. Prevalence has increased since then. In the 1982 statistics prevalence of use in the United States fell in the middle of the international distribution surveyed: rates for past-year prevalence of use varied from 17.6% in Belgium to 7.4% in the Netherlands. (Balter et al 1984)[61]. Even at normal anxiolytic or hypnotic doses, chronic users of these drugs develop tolerance and dependence, and a withdrawal syndrome similar to the alcohol/barbiturate type ensues on abrupt discontinuation, as earlier reported for meprobamate (supra).

Prospective studies on chronic sedative/tranquilizer drug users are complicated by the patient's unavailability to research methods before they start using the drugs. Barker et al (2005)[62] employed in the alternative a case-matching design in studying a cohort of twenty participants evaluated after withdrawal from benzodiazepines, comparing each participants' neuropsychological test performance to that of two (one "anxious" and one "non-anxious", both psychometrically defined) age, sex, and education matched control subjects who had never used sedative tranquilizer drugs. Mean duration of drug use in the patient group was 108 months, and the battery of neuropsychological tests was administered at a mean of 42 months after drug withdrawal. Their results indicated that long-term benzodiazepine use may lead to impairments in the areas of *verbal memory*, *motor control/performance*, and *nonverbal memory* but not *visuospatial skills* and *attention/concentration*. This finding contrasts with the acute measured effect of sedative tranquilizer use on performance testing (see above, Thompson *et al* 1999), under which both attention/concentration and visuospatial memory was found to be impaired. In view of the length of abstinence, their findings indicate that these impairments persist well beyond cessation of benzodiazepine use. However, observed impairments in the area of non-

verbal memory were not solely attributable to benzodiazepine use and may have been influenced by the elevated anxiety levels present in both the case group and the anxious control group.

Other studies that compared neuropsychological performance during treatment and after graded withdrawal have found different results. Some found improvements in task performance measuring attention, vigilance, and speed of information processing, as in the report of Sokol & Power (1988)[63] who studied 12 long-term benzodiazepine users (mean 9 years). Such studies have been criticized however on grounds of poor execution and design. Sokol and Power, for instance, tested only 7 of the patients at 4 weeks of withdrawal, when not all subjects were drug-free.

Rickels et al (1999)[64] compared two groups of chronic (8 year) benzodiazepine users: one group who had successfully withdrawn and one who had not. They reported that successful taper patients (drug-free) performed better on a digit-symbol substitution task and a symbol copy task, and, furthermore, were observed to be more alert, more relaxed, and less anxious than those still taking the drug.

Salzman et al (1992)[65] reported recovery of impaired cognitive function in 13 nursing home residents withdrawn from their benzodiazepine medication, compared with a control group of 12 who did not withdraw. The authors also reported a significant improvement in short-term memory as measured by the digit span and vigilance test methods, which improvement was readily apparent to staff and family members: withdrawn patients appearing brighter, less dysphoric, more energetic and more intellectually alert.

More definitively, however, Barker et al (2004)[66] performed a meta-analysis of published research on the subject of sedative tranquilizer effects, surveying 34 articles published between 1980 and 2000, of which 15 met all inclusion eligibility criteria. They found that previous long-term benzodiazepine users appeared to improve in tested cognitive function in all domains examined, with indications that as age increases post-withdrawal the patient's recovery decreases on tasks of attention/concentration. As to the degree of improvement: where studies employed a within-subject design it was possible to ask the question: *"are previous long-term benzodiazepine users still impaired at follow-up compared to*

controls or normative data?" Mean duration of drug use in this data set was 8.9 years and the median drug-free period was 3 months. They concluded that compared to normals or controls, patients who had withdrawn from long-term benzodiazepine use continued to perform more poorly in most areas of cognition than did controls or normative data except for sensory processing. The residual cognitive impairment resulting from chronic benzodiazepine use is therefore measurable after three months of drug-free living.

Involuntary intoxication

Involuntary intoxication occurs when an individual becomes inebriated or intoxicated on a drug that they consumed unknowingly or, if knowingly, without knowledge or warning of the drug's likely effect. Involuntary intoxication can occur, for instance, if a pharmacist inadvertently dispenses the wrong drug in error to a patient, or if the physician negligently prescribes the wrong drug in error. The intoxication resulting from surreptitious drugging of an unknowing victim is of course also 'involuntary.' The victim of involuntary intoxication may claim to have been assaulted, and misbehavior they engage in as a result of such victimization is not their fault but resides, rather, with the administrator or provider of the drug causing the intoxication that resulted in the misbehavior. The rare phenomenon of "*pathological intoxication*" can be considered a special case of *involuntary intoxication*. In pathological intoxication the subject has a heightened sensitivity to inebriation on a drug, usually alcohol, and becomes excessively intoxicated after voluntary consumption of a small amount, sometimes as little as a single drink. The essence of the diagnosis of pathological intoxication lies in the idiosyncratic state of heightened vulnerability to the drug. For this to be intoxication to be considered involuntary, however, the subject would need to have been unaware of their idiosyncratic vulnerability.

Common claims of involuntary intoxication involving tranquilizing drugs are rarely clear-cut, however, particularly when amnesia is involved, and often result from a patient knowingly consuming alcohol with a properly prescribed $GABA_A$ tranquilizer or hypnotic, with disastrous consequences resulting from the combination. If the patient was truly given no warning of an adverse interaction then a claim of involun-

tary intoxication may be validly made, yet this can be difficult to prove or disprove and the situation contrasts markedly from that where both of the interacting drugs are medically prescribed (an opiate and a benzodiazepine, for instance, taken for the first time) and responsibility for giving notice is well defined at the physician and pharmacist level.

Involuntary intoxication also occurs where an inappropriate drug is improperly mandated by law or compulsory process to be taken by a patient against their will. In the Texas death penalty trial of Ernest Ray Willis the defendant's drugged and unresponsive demeanor in the court room was cited by the prosecutor to illustrate to the jury that Willis was cold, calculating and disdainful of the court and the jury. There was no medical reason for this prescription and Willis, who was innocent (the offense was committed by another, who confessed), was too obtunded by the drug to offer any assistance in his defense. Willis' conviction was overturned, and he was released, 17 years later.

Tranquilizing drugs are also used to involuntarily pacify agitated patients and nursing-home residents, often more for staff convenience than the patient's medical need. Since benzodiazepines exacerbate the cognitive confusion of the dementias, forensic questions may be raised regarding the patient's competence to sign wills and other instruments under tranquilizing drug influence.

The future of tranquilizing drugs

According to a 2006 pharmaceutical industry business report (Business Wire 2006)[67] addressing the hypnotics market and the future drug pipeline: *"the insomnia market has been dominated by Ambien (zolpidem), Sonata (zaleplon) and Imovane (zopiclone), and the older hypnotics such as benzodiazepines. However, the global insomnia market is set to grow from $3.7 billion in 2005 to $5.5 billion by 2014 driven primarily by the launch and adoption of Lunesta (eszopiclone), Rozerem (ramelteon) and Ambien CR as well as pipeline drugs from 2006 onwards"*

Ambien had U.S. revenues of $2 billion in 2004 but faced competition from recently launched hypnotics, and the drug became generic in 2006, its revenue evaporating. In an attempt to hold onto the residue of the market Sanofi-Aventis launched a sustained-release form (Ambien CR) in the USA in October 2005 yet the Ambien franchise was predicted to decline from 2006 onwards to approximately half the value it is today by 2014.

The industry's "prospective players" [pharmaceutical manufacturers] were warned that by 2014 stiff competition is to be expected from numerous generics, worth nearly US$800 million, as well as a number of non-GABA$_A$, non-scheduled hypnotics with revenues topping US$700 million. In such a crowded market, *"innovation is key and product differentiation, demonstration of cost-effectiveness and niche strategies are essential."*

The report identified such a niche, a new sub-market within the user population, the *"transient insomniac"* which population, they reported:

"…is severely under served, and presents an ideal niche for manufacturers. If manufacturers can increase the proportion of individuals using prescription hypnotics at least a few nights a month, to the level of those who use them at least a few times a week, usage of prescription hypnotics could increase by 50%."

Of the hypnotic drugs currently at the forefront of the market only Rozerem (ramelton) does not stimulate the GABA$_A$ receptor, but relies on the melatonin system. A novel and under-explored target for tranquilizer drug action at the GABA$_A$ complex is the neurosteroid receptor (see **Fig 1**). The industry has previously marketed drugs which act directly at this locus, such as Althesin, a mixture of two neurosteroids: alphaxolone and alphadolone, sold as a surgical sedative. It was withdrawn from human use in 1984 due to toxic reactions and has now been 're-branded' for veterinary use under the name "Saffan". Current research is directed however not at direct stimulation of the GABA$_A$ receptor complex' neurosteroid receptor but at stimulating production of the brain's own enurosteroid neurotransmitter(s), in the hope that endogenous regulatory processes will prevent tolerance and dependence from developing. One such compound, currently known as "XBD173" is in the pipeline and shows antipanic effects in animals – apparently without sedation and tolerance (Ruprecht et al 2009)[68]. Similar safety claims, of course, were previously made for the barbiturates, carbamates, benzodiazepines and z-drugs. Only time will tell, yet the history of the field suggests that if the drug gets to market, humans will find some way to abuse it, and forensic examiners will be dealing with its adverse effects.

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