Fifty Years of Research into the Pharmacology and Toxicology of Drugs other than Alcohol with reference to Traffic Safety

de Gier, J.J.

Department of Pharmacoepidemiology & Pharmacotherapy, Faculty of Pharmacy, University of Utrecht, PO Box 80082, 3508 TB Utrecht, The Netherlands

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Abstract

This paper will describe some but not all of the highlights in the pharmacology and toxicology of psychotropic substances and explain why future discussions on the use of drugs other than alcohol by drivers will be influenced by recent advances as they can presently be judged.
The approach to fifty years of research will be based primarily on discussing the link between human brain and traffic safety and to describe the exciting world of psychopharmacology. This will help us to understand how the human brain under the influence of psychotropic substances is able to affect our behaviour and skills, especially those relating to driving, and thereby affect traffic safety. It is important to realise that recent advances in psychopharmacology will eventually guide us to new classes of drugs, which will be therapeutically superior to old psychotropic medicines because of their lack of unwanted side-effects such as dependence, amnesia and sedation.
In reviewing the proceedings of ICADTS conferences over the last decades one can observe the trends in research that support the development of safer drugs for drivers. The exercise clearly shows that ICADTS conferences focussed a great deal on administrative aspects, law enforcement, legal issues relating to drugs other than alcohol and traffic safety. Recently the emphasis in this area has been focussed on changing traffic laws in various European countries to allow law enforcement officers to concentrate more on illicit drug use by drivers. This major step forward in combating drugs and driving has been facilitated by advances in the field of (analytical) toxicology, where the development of on-site devices for screening saliva and urine samples has resulted in the introduction of effective, affordable and easy to use non-instrumental devices. This development will eventually lead to more awareness and understanding of the prevalence of illicit drugs in road traffic.
The conclusion is that fifty years of research efforts in the field of drugs and driving has made major contributions to improving traffic safety, although studies to support this view are still lacking.

Introduction

In discussing fifty years of research into the pharmacology and toxicology of drugs other than alcohol, one has to decide what approach will be most feasible in focussing on traffic safety. It is obvious that two approaches can be followed. First, to review the literature and describe the advances in pharmacology and toxicology and show what scientists contributed to their field of medicine and decide how that would relate to traffic safety. However, this would have been the start of a whole book on traffic medicine which was beyond the scope of this paper. A second approach would be to look for an approach in which the link between human brain and traffic safety is clear when discussing the effects of drugs other than alcohol. In this way

it would be possible to describe the exciting world of psychopharmacology that will help us to understand how the human brain under the influence of psychotropic substances is able to affect our behaviour and skills, especially those relating to driving and thereby affect traffic safety. It is important to realise that recent advances in psychopharmacology will eventually guide us to new classes of drugs that are therapeutically superior to the old psychotropic medicines because of their lack of unwanted side effects such as dependence, amnesia and sedation (1).
Besides interest in advances in pharmacology, the field of toxicology has offered new and exciting opportunities for the development of on-site devices for screening saliva and urine samples of road users in order to detect the presence of illicit drugs. These devices have been instrumental in changing road traffic laws in several European countries, such as Germany, Belgium and Sweden, allowing law enforcement officers to focus more on illicit drugs. This contribution to more awareness and understanding of the prevalence of illicit drugs in road users will have an impact on attitudes in our society towards the use of these drugs in road traffic.
This paper will describe some though not all of the highlights in the pharmacology and toxicology of psychotropic substances and explain why future discussions on the use of drugs other than alcohol in drivers will be influenced by those recent advances as they can presently be judged.

Focus on drugs other than alcohol in ICADTS Conferences
In the past ICADTS conferences have been dedicated to different topics concerning drugs other than alcohol. In the last two decades, since 1980 (the Stockholm conference), more than 250 papers have been published in ICADTS conference proceedings focussing on various issues, such as studies on prevalence among drivers, analytical aspects and drug screening, effects on skills and performance and experimental design, and administrative, legal and medical aspects (see Table 1).

Table 1 Papers on Drugs other than Alcohol in ICADTS Conferences (1980-1997).

ICADTS Conference (Total number of papers)	*Papers dedicated to*				*Total number of papers on drugs other than alcohol (%)*
	Prevalence among drivers (general, injured, killed)	*Analytical/ drug screening (procedures and test devices)*	*Effects on skills/ Performance/ Experimental design*	*Administrative /legal and medical aspects*	
T80 (115)	10	7	7	4	28 (24%)
T83 (141)	3	5	10	2	20 (14%)
T86 (114)	10	3	10	12	35 (31%)
T89 (154)	13	1	9	7	30 (19%)
T92 (220)	10	8	19	16	53 (24%)
T95 (154)	13	7	5	18	43 (28%)
T97 (248)	13	8	10	17	48 (19%)
Total (1146)	*72*	*39*	*70*	*76*	*257 (22.7%)*

A total of 257 papers have been presented since 1980 and on average 22.7% of all papers presented at ICADTS conferences have been dedicated to discussing the various issues relating to drugs other than alcohol and traffic safety. There has been an increasing trend at the last two conferences towards focussing on administrative, legal and medical aspects. This reflects to some extent the interest that has been given to preparing amendments to road traffic laws in Germany (1998), Belgium and Sweden (1999) with respect to a zero-limit regulation for certain illicit drugs. This trend will certainly continue to grow and other European countries are likely to implement roadside screening as soon as effective, affordable devices are introduced during the next few years (2). It is expected that in forthcoming ICADTS conferences evaluations of these changes will be presented as well, offering future participants new information to help them understand how amendments to traffic laws can have an impact on traffic safety.

There are, however, several more issues to discuss in these future conferences. First of all it should be clear whether a discussion on the use of drugs in society in general, including health care and social issues, will have to be considered in a discussion on drug use and road safety. It is obvious that approaches to solving problems in society with respect to illicit drug use and to improving prescribing and dispensing practice when it comes to psychotropic medication, must be a multi-disciplinary effort, involving all those who are responsible for people's health and well-being. Another issue for further discussion in future conferences will be the relative importance of focussing on illicit drug use in drivers. In most large-scale epidemiological surveys among drivers (in general driver populations, and DUI suspected or collision involved drivers) it has been indicated quiet clearly that the prevalence of certain psychotropic licit or medicinal drugs is higher than found for illicit drugs (3). ICADTS has been instrumental in discussing these issues in the past and has created several opportunities of becoming more influential in future talks with policymakers and health care professionals and has involved its members in various working groups. The strategy should be to involve those with state-of-the-art knowledge and valuable experiences, representing different disciplines in our society, in the efforts to present guidelines for implementing their knowledge in practice. Society has been asking for more emphasis on applying current knowledge and it is obvious that this need should be given priority in future discussions at ICADTS meetings.

Advances in psychopharmacology

It is interesting to note that in the early 1950s a new area of medicine arose from the discovery of so-called 'modern' psychotropic medicines used to treat mental illness. The chemical structure of some of these drugs had been described many years before. For example in the early 1950s a new area of medicine arose as a result of benzodiazepines described by Sternbach in the 1930s. The clinical efficacy of these medicines started to become significant after conducting the first clinical trials in the 1960s. It was in those years that a new branch of pharmacology was introduced which today we call the field of 'psychopharmacology'. It has resulted in what we now know as one of the most rapidly advancing fields of medicine. The scope of this field is not only confined to medicines, since other chemical substances are being used to study the functions of the brain in health and disease.

This paper will deal with a brief synopsis of the most important discoveries in psychopharmacology with emphasis on understanding how new drugs can contribute to the safety of those who use them as a treatment. There are many good texts available to explain the functional neuroanatomy of the brain, and the basic aspects of neurotransmitter function, as well as drug treatment in various psychiatric disorders (1). It is beyond the scope of this paper to even try to summarise these, so that highlights will be discussed in brief.

The concept of chemical transmission in the nervous system arose in the early years of the century. The physiologist Sherrington proposed that nerve cells communicated with one another by liberating the neurotransmitter into the space or synapse in the immediate vicinity of the nerve ending. While it was assumed that the brain contained two transmitters (acetylcholine and noradrenaline) it was only in the early 1950s that experimental evidence indicated that there were many more types of transmitters in the brain. Today more than 35 different types of neurotransmitter have been found in the human brain and several more are added to the list every year. Neurotransmitters can either excite or inhibit the activity of a cell with which they are in contact, mostly by activating a specific receptor in various parts of the brain. By activation or inactivation of channels for different ions (sodium, potassium, chloride) in the receptor site neurotransmitters can produce potentials across the nerve cell membrane and thereby control cellular events.

How can psychotropic drugs affect the neurotransmitter in the brain? Since neurotransmitters are presumed to be of fundamental importance in the aetiology of psychiatric and neurological disease, these substances have been the target of attention for explaining how these drugs act. A common mechanism appears to exist for the synthesis, release, storage and metabolism of these transmitters. The action of psychotropic drugs can be explained in general terms by their effects on some of these processes. The most frequent action of psychotropic drugs that modify synaptic transmission involves an activation or inhibition of postsynaptic receptors. They occupy a receptor and act as an agonist or antagonist for that receptor, respectively producing activation or reduction of the transmission. Sometimes drugs have their own receptor site which forms part of the receptor complex for a given transmitter. This can cause a conformational change in the receptor and thereby can increase its sensitivity to the action of the transmitter. For example benzodiazepines (the most widely used psychotropic medicines for treating anxiety and insomnia) occupy a specific benzodiazepine receptor which forms a part of the GABA-A receptor thereby increasing the action of GABA (gamma-aminobutyric acid) in the brain. As a consequence they affect the activities in the cerebellum (concerned with balance and coordination), the limbic areas of the brain and the cerebral cortex (thought and decision-making, fine movement control). Due to the effects of GABAergic neurons on other neurotransmitter systems in the brain, secondary changes occur in noradrenergic and serotonergic pathways, which may contribute to their anxiolytic effects. They have a short-term action on the central noradrenergic system that may contribute to the sedative effects which most conventional benzodiazapines produce, at least initially. The performance impairing effects of benzodiazepines have been determined in many experimental studies during the last decades and were more recently confirmed in pharmacoepidemiological studies. During the first two weeks of treatment with benzodiazepines, extremely high relative risk ratios (5 to 6 fold increase in accident risk, comparable to the increased risk of alcohol 0.1 % blood alcohol concentration) have been reported (4).
The discovery of benzodiazepine receptors in the brain is an exciting one and would suggest that there are natural ligands present which act on the receptor. To date less than ten endogenous ligands for the benzodiazepine receptor have been isolated that show agonist or inverse agonist activity, but one specific compound has not been identified yet. There is some evidence to suggest that anxiety arises as a consequence either of a deficiency of an endogenous agonist or the presence of an endogenous inverse agonist. A possible strategy that will yield new compounds may be the development of drugs that either facilitate the synthesis of endogenous agonists or reduce the synthesis of inverse agonists.
Several new anxiolytic drugs act at the benzodiazepine receptor site even though the chemical structure of these molecules differs substantially from the benzodiazepines. One of the first

was zopiclone (a cyclopyrrolone) which did not prove to be superior compared to benzodiazepines with respect to impairing effects on driving skills. A structurally somewhat similar molecule zolpidem has also been marketed as a hypnotic, and relatively safe for drivers (5). Other compounds that have been introduced are a beta-carboline, abercanil, and a new benzodiazepine, the tetracyclic 2,4 benzodiazepine bretazenil, which has been introduced as a short acting sedative-hypnotic.
Other strategies have been followed in designing drugs in which the adverse effects of the "classical" benzodiazepines could be reduced but at the same time have their beneficial effects maintained. A novel group has been introduced which, unlike the benzodiazepines, do not facilitate GABAergic function but act as agonist at the 5-HT1A receptors: buspirone, gepirone and ipsapirone. Clinical trials with buspirone have shown that the drug is slow in onset of action compared to diazepam, but it produces significantly less sedation and fewer detrimental effects on psychomotor performance than benzodiazepines. Buspirone did not affect the driving of anxious patients who drove a car in an actual driving test (6).
During the last two decades there has been a major effort by the pharmaceutical industry to develop drugs that have a high degree of selectivity for the serotonin transport site in the brain. Selective serotonin re-uptake inhibitors (SSRIs) are widely used for the treatment of depression and their behavioural toxicity, as indicated by their effects on psychomotor performance and driving skills, is much more favourable for drivers when compared with the older tricyclic antidepressants (7,8).

A similar effort during the last two decades has been made to develop a second generation histamine H1-receptor antagonists, the so-called 'nonsedating' antihistamines. They have high potency and additional anti-allergic properties as well as H1 antagonism but are associated with fewer adverse effects compared with the first generation antihistamines. All of these newer drugs have a more favourable risk-benefit ratio with regard to the adverse effects on the central nervous system (CNS). Although the second generation are called 'nonsedating' some of them are not entirely devoid of CNS activity (9). Actual driving studies have shown that the behavioural toxicity of many second generation antihistamines is lacking in recommended doses, and therefore relatively safe for drivers (10,11).

Research in psychopharmacology with respect to drugs of abuse is mainly focussed on treatment options for drug dependence. Hyperactivity of the dopaminergic system in the brain would appear to be of crucial importance in causing drug dependence in most classes of drugs of abuse. Most drugs of abuse that cause an elevation of mood which is the basis of a positive reinforcement bring about the release of dopamine. But other systems of neurotransmitters are involved. For example opioid withdrawal is associated with a profound change in noradrenergic activity and excessive sympathetic activity (anxiety, tremor, sweating, hypertension). A malfunctioning of the serotoninergic system may play an important role in predisposing people to drug abuse, while drugs such as the SSRIs may have an important role to play in the rehabilitation of some types of drug dependence (for example alcoholism). Major advances have been made in the neurobiological basis of drug dependence with the application of new techniques (neuroimaging) which allows the brain to be studied in conscious state and new treatments with potential agonists on the receptors that are important for drug reinforcement or withdrawal to be evaluated.

The opioids (the term narcotic analgesics is obsolete, it was formerly used to describe potent opioid analgesics which had sedative properties) produce their pharmacological effect by interacting with a closely related group of peptide receptors (mu 1 and 2, kappa, delta), thereby suggesting that endogenous opioid-like peptides exist, with some physiological function. The discovery of the various types of opioid receptors will probably lead to the

development of different types of drugs that have potent centrally acting activity but do not have an abuse potential.

The psychostimulants (amphetamines(-like drugs) , cocaine) cause subjective effects that depend on the dose of the drug and the route of administration, the personality of the individual and the environment in which they are administered. For these drugs as for 'designer drugs' and hallucinogens, also called psychedelics or psychotomimetics, pharmacological and toxicological knowledge has been used to describe their effects in 'normal' and toxic doses in humans. The effects are obviously not compatible with safe driving. Although most countries have laws that treat consumption and possession of small amount of drugs in different ways, they have demonstrated the political will to put the potential right of the individual to consume drugs behind the public's right to safe road traffic. The goal of drug-free traffic has not stimulated experimental studies to determine illicit drugs' effects on driving performance or skills related to driving. These studies are hardly known except for cannabis. It is interesting to discover that more than one hundred years ago one of the drugs for treating psychiatric illnesses in those days, known as hashish, is still at the focal point of our attention, however, no longer primarily for use as medicinal drug but as illicit drug. Several empirical studies have been undertaken to determine the separate and combined effects of delta-9-tetrahydrocannabinol (THC) and alcohol on actual driving performance (12,13). THC doses of 100 µg/kg and 200 µg/kg and alcohol given in doses to sustain 0.04 % blood alcohol concentration significantly impair the subject's road tracking and car following performances. The magnitude of the mean effects were minor after alcohol and the low dose of THC and moderate after the higher dose of THC. Both THC doses in combination with alcohol severely impaired the subject's performance in both tests. The effects of THC in a dose of 200 µg/kg when combined with a moderate dose of alcohol become severe and may constitute unacceptable risks in traffic.

It is obvious that research efforts in psychopharmacology will primarily support the view that medicinal drugs for treating patients with psychiatric or neurological disorders will become safer in coming years, e.g. with a therapeutic advantage over the existing drugs and without any sedative or other impairing effects on driving, even without any interactions with alcohol. For illicit drugs new knowledge in psychopharmacology will primarily derive from describing the effects of 'new chemical compounds'. In treating drug dependence advances in psychopharmacology will lead to new drugs and a better understanding of genetic predisposition based on characteristics of the nervous system.

Advances in toxicology

The enforcement of traffic laws pertaining to the use of drugs by drivers depends on the legal and practical provisions for the police to check drivers' fitness to drive. From an international perspective, screening devices have not yet become common in drug driving enforcement. Police practice with screening devices is not without problems (2). It is inconvenient to obtain sweat or urine samples from drivers at the roadside and often high refusal rates in urine testing, exceeding that for blood testing, have been experienced. However, it is the advance in analytical toxicology that has provided us with a wide variety of screening devices and it can be expected that roadside drug screening will increase as soon as reliable and effective devices are introduced at an affordable price. It is with this goal in mind that the EU's Directorate General for Transport (DG VII) sponsored a contract to allow a group of toxicologists to make an inventory of state-of-the-art road side drug screening devices (also known as the ROSITA project) and to evaluate their performances (accuracy values, ease-of-

use, etc.). The report has been published recently and included 19 non-instrumental devices, of which 16 were designed for screening urine samples, 3 were designed for saliva and one of these can also be applied to sweat (14). The main problem issues are difficult interpretation of results, detection of ecstasy and other designer amphetamines, and the specificity of the tests for the illicit amphetamines and morphine. Some reliable devices were selected allowing suitable drug screening devices to be used in future efforts to improve law enforcement with respect to drug drivers.

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