Polish Journal of Pharmacology
Pol. J. Pharmacol., 2001, 53, 415–434
ISSN 1230-6002

REVIEW

DRUG ADDICTION. *PART III.* PHARMACOTHERAPY OF ADDICTION

Jerzy Vetulani

Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Drug addiction. Part III. Pharmacotherapy of addiction. J. VETULANI. Pol. J. Pharmacol., 2001, 53, 415–434.

The last decade brought a considerable progress in pharmacotherapy of addiction. Basing on recently gained knowledge of mechanisms of development of addiction and the physiology of the brain reward system, several therapeutic strategies have evolved. The strategies aimed at targeting the basic mechanisms of addiction rely on the premises that addiction is caused by adaptive changes in the central nervous system and that craving, which is the main cause of relapse, depends on dopaminergic mechanisms and requires high general excitability. The pharmacological approach involves drugs that reduce neuronal adaptability by inhibiting the calcium entry to neurons both through voltage-gated channels (e.g. nimodipine) and NMDA receptors (e.g. memantine), and drugs that stimulate the inhibitory GABAergic system (γ-vinyl-GABA, baclofen), Particular attention is paid to the compounds that may attenuate dopaminergic hyperactivity, without considerable suppression of tonic activity of dopaminergic neurons (e.g. BP 897, a partial dopamine D_3 receptor antagonist). Specific strategies are aimed at interference with the action of particular drugs of addiction. An important group includes the agonistic therapies (known also as substitution or maintenance therapies) in which a long-acting agonist is used in order to reduce the action of the drugs of high addictive potential (e.g. methadone against heroin addiction or vanoxerine (GBR 12909) against psychostimulants). Other specific strategies aimed at reduction of the transport of molecules of addictive substances into the brain: the approaches involve preparation of antibodies that form complexes unable to cross blood-brain barrier or enzymes accelerating the metabolism of the compounds in the blood (e.g. variants of butyrylcholinesterase). A considerable progress has been made in combating the abuse of legal addictive substances, alcohol (naltrexone, acamprosate) and tobacco (bupropion). The prospects for developing effective pharmacotherapies against addiction are bright. Unfortunately, ideological and social implications, as well as the conflict of interest with illegal narcotic manufacturers and distributors, may considerably hamper the progress in combating addiction (e.g. difficulties in introduction of methadone).

Key words: *addiction pharmacotherapy, addictive stimulants, antiaddiction vaccines, legal psychotropic substances, general antiaddictive strategies, specific antiaddictive strategies*

Present understanding that drug addiction is a chronic brain disease paves the way for pharmacotherapy. Its ideal goal is to enable a patient to maintain permanent, voluntary abstinence. However, this goal has been attained very rarely, so we have to be satisfied with provisional goals, such as reduced drug use, improvement of patient's functioning in the society, and minimization of addiction-related health and social hazards. Surprisingly, the conviction that addiction treatment does not require medication (beyond detoxification period) still prevailed at the end of 20th century. For instance, in the USA, where 700,000 alcoholics are subjected daily to various forms of treatment, three behavioral techniques, i.e. cognitive-behavioral therapy, motivational enhancement therapy and Anonymous Alcoholics Program or similar twelve-stage programs, are still considered the most important types of therapy. Of pharmacotherapeutic measures, that all are regarded as no more than adjunct procedures, only the deterrent therapy with disulfiram, considered barbarian in Europe, has been adopted [40]. The belief in effectiveness of pharmacotherapy is presently surprisingly scarce: a 1999 survey among staff members in American institutions caring for addicts revealed that only 39% and 34%, respectively, endorsed the increased use of naltrexone and methadone maintenance [36]. Nevertheless, in spite of considerable resistance, pharmacotherapeutical approach is gaining popularity. Apparently, as mentioned earlier [139], it is the most cost-efficient solution, which in the case of treatment of heroin addicts with methadone brings a ten-fold reduction of the costs of addict's maintenance.

Interest and progress in the studies on anti-addictive drugs, avalanching over the last twenty years, lets us strongly hope that in the present century pharmacotherapy will significantly limit the addiction plague. However, as we will discuss later, we cannot exclude that we will be yet caught by unpleasant surprises along this way.

Each addiction-forming substance interacts directly with its molecular target, such as dopamine transporter, opioidergic and nicotinic receptors, etc., but also it may influence basic mechanisms of the reward system, associated principally with the phenomenon of drug craving. Extensive research led to the discovery of both, drugs effective against specific addictions (e.g. nicotine patches in smoking-cessation therapy, methadone in heroine addicts), and compounds with more general action profile. Since concomitant addiction to many substances (polyusage) is unfortunately on the rise, it seems that future belongs to the drugs acting precisely on dopaminergic system, striking directly the very essence of addiction process, craving.

As discussed before [140], addiction may often be linked with congenital aberrations of the reward system, and adaptive changes in the brain functional systems, triggered by chronic drug use. These changes can, at least partly, involve the formation of memory traces [30, 53, 109]. The changes are closely connected with calcium ion influx into nervous cells and activation of numerous intracellular processes. Thus, it appears that the tactic aimed at a search for anti-addictive drugs with an universal profile should focus on looking for the compounds, which properly inhibit dopamine receptors in the limbic system, and blockers of calcium ion influx into neurons. Alternatively to the blockade of stimulatory systems connected with calcium ion influx into neurons, the strategy attempting to activate inhibitory mechanisms, associated with chloride ion influx into neurons (stimulation of inhibitory GABA-ergic system) can also be considered.

Beside these general strategies, there are also tactics to cope with specific groups of addictions. In several cases, pharmacotherapy based on drug interaction with specific receptors conveying the effects of individual substances has been proposed. It encompasses so-called substitutive therapies, utilizing agonists to block receptor sites activated by addictive drugs. It includes also efforts to apply peripherally acting compounds, such as anti-cocaine and anti-phencyclidine vaccines, that block the excess of addictive substances to the brain. Finally, there are certain specific types of therapy of addiction, found to be effective in treatment of addiction to legal substances of abuse. The examples are naltrexone and acamprosate treatment in alcoholism, and bupropion therapy in nicotinism.

DRUGS FOR DRUG ADDICTION

Drugs influencing dopaminergic system

In the light of dopaminergic theory of drug addiction, dopamine receptor blockade with neuroleptics might appear the most efficient method of pharmacotherapy. However, such treatment is ineffective since neuroleptics are strongly aversive,

probably just due to dopaminergic system blockade, and the patients refuse to use them. Fortunately, some dopaminergic system-influencing drugs were proved to decrease drug craving, and without evoking aversion.

Partial D_3 receptor antagonists – the compound BP897

An ideal drug addiction medication should effect permanent lack of drug craving in former addicts. Such medication may be most probably found among compounds that affect dopaminergic systems involved in wanting, in the drug craving phase. As mentioned earlier [140], craving is the cardinal feature of drug addiction, and precisely it should be targeted by drug addiction pharmacotherapy, since craving is responsible for drug abuse reinstatement. Despite 15-year intensive research, truly effective anti-craving medication for addiction to cocaine, the "purest" addiction-forming compound acting directly on dopaminergic system by dopamine transporter inhibition, has not been found yet. Some hope that we are approaching a breakthrough arose in the last years. Assuming that D_3 dopamine receptor is implicated in drug addiction, Pilla et al. [98] synthesized N-{4-[4-(2-methoxyphenyl)-1-piperazinyl]-butyl}naphthalene-2-carboxamide, known under the code name BP897, a partial antagonist of rat dopamine D_3 receptor. Due to the fact that both excessive and inadequate stimulation of the reward system evokes craving, partial dopamine receptor antagonists seem to be the most promising compounds: they will stimulate receptors upon neurotransmitter deficit and inhibit them in case of its excess. BP897 was shown to inhibit cocaine seeking in cocaine-dependent mice [98] and rats [105]. In rhesus monkeys, administration of BP897 reduced self-administration of cocaine or D-amphetamine, and the fact that the compound is not self-administered indicates that BP897 has no intrinsic, primary rewarding effects, and therefore has a profile of activity suitable for consideration as a potential treatment for cocaine dependence disorder [9]. Although later studies have shown that BP897 acts *in vivo* and *in vitro* as an antagonist of human dopamine D_3 receptor [147], the compound, after preclinical trials carried out in Cambridge University and INSERM, has recently been under investigation by Bioprojet and entered phase I trial for the potential treatment of drug craving and vulnerability to relapse that are elicited by drug-associated environmental stimuli [105].

Possibly, BP897-resembling compounds will be suitable for the application in the therapy of addiction to other drugs, and also to combat craving not associated with drugs but with inadequate response to natural rewards. In the latter case, dopamine release is much lower than in the course of high dosing of addictive drugs, and perhaps partial D_3 dopamine receptor agonists will compensate for significant deviation from the normal values. Such imbalance has been observed especially as hyperphagia in obese subjects. These patients can refrain from chips and chocolate eating for a long time, but if a bag with chips has been opened and the first chip has been consumed (priming), they usually are unable to resist eating a whole bag. Therapeutic agents similar to BP897 could be helpful in such situations.

Hopes and reservations raised by the compound BP897 and related D_3 receptor antagonists have been reviewed in detail both in scientific journals [20, 105] and newspapers [148].

Drugs inhibiting calcium influx into the cell

Calcium ion plays a crucial role in cell function. It can enter a normal cell through membrane channels, belonging to two classes: voltage-dependent and ligand-dependent ones. Numerous functions of calcium ions comprise their basic role in the mechanisms of plasticity and adaptation of the nervous tissue. Thus, the blockade of physiological mechanisms of calcium influx into the cell can impair the ability of the nervous system to plastically change in response to chronic drug action, including adaptive changes underlying addiction development [138].

L-type calcium channel blockers

Among a multitude of voltage-sensitive calcium channels, L-type calcium channels appear to play a principal role in the regulation of adaptive changes in the central nervous system [138]. The blockers of these channels are interesting for their potential application as anti-addictive agents, since their introduction to clinic would be easy, as they have long been used in medical practice to treat circulatory disorders. As their pharmacology and side effects in humans have been well documented, in

case they are found effective in drug addiction treatment, their introduction for clinical use will be much simpler in comparison with the compounds hitherto not yet used in humans.

L-type calcium channel blockade abolished expression and development of opiate addiction in rats [4, 5, 84]. Rewarding properties of morphine, cocaine and amphetamine were also blocked, which was demonstrated using place preference test and self-administration test [14, 62, 64, 65]. In some cases, beneficial effects were observed following joint administration of isradipine, a calcium channel blocker, and naltrexone, an opiate receptor blocker. This combination blocked rewarding cocaine and alcohol actions [25]. Calcium channel blockers themselves did not block alcohol-conditioned place preference [14]. All these reports along with the demonstration that ionophore Bay K-8644, which facilitates calcium influx into the cell, appears to enhance rewarding properties of morphine [63], suggest that the blockers of calcium influx into the cell through L-type channels could be applied in drug addiction treatment. However, relevant studies have been seriously delayed by a single communication, never confirmed later, claiming that nifedipine evokes confusion in morphine-dependent patients. Although this study dealt with a quite extreme situation, when abstinence symptoms were evoked by naltrexone administration in 2 addicted individuals, it was sufficient for the authors to warn seriously against application of calcium channel blockers in the treatment of drug addiction [124]. This report has often been cited by researchers engaged in the search for different substances which could be used in drug addiction treatment, such as NMDA channel blockers. They generally do not mention that clinical trials proved that chronic nimodipine treatment could alleviate cognitive disturbances in morphine, cocaine, alcohol and marihuana polyusers [50], and that nifedipine decreased subjective cocaine-induced effects in humans [85]. Thus, it appears that initial fears were not firmly justified, the more so that calcium channel blockers have been introduced into clinical practice due to their other interaction with opiates, as they augment their antinociceptive effect and decrease tolerance to this action. This was demonstrated many times in animal experiments [5, 31, 84, 129]. These results have been applied in clinical practice, since it was shown that nimodipine co-administration with morphine mitigated the necessity of morphine dose escalation in a majority of the patients suffering from terminal neoplastic disease, and enabled dose reduction by half [117]. The authors conclude that calcium channel blockade suppresses the development or expression of morphine tolerance in a clinically significant manner. Furthermore, epidural nifedipine administration in the patients experiencing postoperative pain quadruplicated duration of action of the standard morphine dose [96]. However, another recent study did not demonstrate any influence of nimodipine or nifedipine on morphine consumption after colorectal surgery [154]. As L-type calcium channel blockers did not change morphine effects in healthy volunteers [46], the possible usefulness of drugs influencing calcium channels as enhancers of morphine analgesia remains disputable.

NMDA receptor blockers

NMDA receptor is a second gate allowing calcium entry into neurons. It is characterized by a very complex structure, having several regulatory sites, determining its permeability for calcium ions. This is why there are numerous classes of NMDA channel antagonists, which block either glutamate binding site (competitive antagonists) or others, e.g. glycine binding site [27].

Various types of NMDA receptor antagonists: competitive, noncompetitive and glycine site antagonists, suppress development and expression of opiate abstinence syndrome to different degrees [99, 132]. The results of the studies of Popik and Skolnick on memantine [104] and of Popik and Kolasiewicz on a competitive NMDA receptor antagonist, the compound NPC 17742 (2R,4R,5S-2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid) [100] have suggested that these compounds can have a potential to counteract relapses, as they abolished drug seeking by drug-dependent mice.

NMDA receptor antagonists inhibit also different kinds of sensitization. They block as well dopamine receptor sensitization induced by chemosympathectomy [26], chronic treatment with directly acting dopaminomimetics [33] and compounds stimulating dopamine receptors indirectly, such as morphine [58] and dopamine releasers and inhibitors of dopamine uptake [59, 91, 107]. The action of dizocilpine, NMDA receptor antagonist, seems to consist in the prevention of sensitization development rather than its expression [149]. Interestingly, dizocilpine inhibits development of sensiti-

zation to various addictive substances, although its administration caused sensitization to its own locomotor effects [150].

NMDA receptor blockers, which have already been introduced into clinical practice because of other indications, seem particularly interesting. Memantine is the first to mention. This drug has been widely used in acute and chronic neurodegenerative diseases, and for the treatment of anxiety and chronic pain. Unlike other NMDA receptor antagonists, memantine at therapeutic doses in dementia does not cause any undesired reactions, resembling those elicited by the competitive NMDA receptor antagonists [95].

NMDA receptor antagonists do not show a uniform anti-addictive effect. For example, they differ in the inhibition of certain cocaine effects [12]. Memantine (but not dizocilpine) suppresses cocaine-conditioned motor response [12], but it does not block cocaine self-administration by rats, triggered by cues associated with its former use (cue-induced craving), the effect being inhibited by another antagonist, D-CPPene [3-(2-carboxypiperazine-4-yl)--1-propenyl-1-phosphonic acid]. Moreover, memantine does not change cocaine priming effect (i.e. the ability of a single cocaine dose to induce drug seeking by rats previously treated with and than withdrawn from cocaine) [13], but it dose-dependently inhibits cocaine self-administration both in constant and increasing-dose paradigm (while dizocilpine increases a number of cocaine self-administration episodes in the latter paradigm) [56].

Memantine suppresses rewarding effects of certain addiction-forming substances. It only insignificantly reduces alcohol drinking [97], but, in contrast to dizocilpine, it inhibits morphine self-administration in mice [122]. It prevents the development of tolerance to morphine analgesia, induced by repeated exposure to the drug [10, 101], and annuls the developed tolerance to morphine [102]

Memantine appears a good candidate for an almost universal anti-addictive medication, but there are some data engendering caution. Namely, high memantine dosing potentiates reinforcing effect of electrical stimulation of the rat brain, although to the lower extent than dizocilpine does [134]. Yet more alarming seems the result of another experiment, even though it comprised a small group of tobacco and crack smokers: memantine enhanced their subjective feeling of pleasure [22].

Ibogaine shows also characteristic features of NMDA receptor antagonist. It incited vivid interest, when it was reported to abolish heroin or cocaine craving in addicted polyusers. Lotsof [70], the discoverer of this effect, patented ibogaine as a universal anti-addictive therapeutic agent. It was recently suggested that ibogaine may exert its anti-addictive effects by reversing the behavioral disinhibitory properties of stimulant drugs, related to their stimulatory action on the neuroendocrine systems [130]. Despite some neurotoxic effects [88, 89] that may be related to its ability to inhibit glutamate uptake by glial cells (as shown for cortical astrocyte cultures from mice and rats) and possibly to enhance the glutamate release from cortical synaptosomes [66], ibogaine does not seem very dangerous, since neurodegeneration neither was described in Gabon inhabitants who commonly use it nor were any harmful ibogaine effects discovered after supplementation with this agent of a tonic beverage, customarily used in France in the sixties (a counterpart of the presently used *Red Bull*) or after its use as a doping agent by sportsmen.

In primates ibogaine is rapidly O-demethylated to form the metabolite 12-hydroxyibogaine (noribogaine) that was found to be a long-lasting and potent biologically active agent. It is more active than its parent compound in increasing extracellular serotonin levels and is approximately 10 times more potent than ibogaine as an indirect serotonin agonist. On the other hand, noribogaine is less potent as a stimulant of corticosterone secretion and appears less apt to produce the adverse effects associated with ibogaine. This suggests that noribogaine may be a safer alternative for anti-addictive medication development [8]. As mentioned above, excellent articles about ibogaine have been published and are available *in extenso* on the internet [99, 103].

Drugs activating GABAergic system

γ-Vinyl-GABA, a GABA transaminase inhibitor

γ-Vinyl-GABA (GVG) is one of the potential anti-addictive drugs. It is an irreversible GABA transaminase inhibitor, so its action increases neuronal GABA level and enhances GABA release. Anti-addictive action of GVG can consist in the indirect activation of inhibitory GABAergic receptors which regulate the activity of dopaminergic neurons in the ventral tegmental area. It was shown that GVG in-

hibited nicotine action, so potentially it can be applied in tobacco smoking cessation therapy [28]. It was also demonstrated to have beneficial effect in cocaine abusers [29]. Recently, GVG has been reported to suppress elevation of the nucleus accumbens dopamine level induced by the administration of addictive substances, such as stimulants (methamphetamine), opioids (heroin) and ethanol [42]. GVG much more efficiently abolishes the effects of heroin and alcohol than those of methamphetamine. GVG is commercially available and has been registered as *Sabril*, *Sabriolex* and *Vigabatrin* [141].

GVG is also used as an antiepileptic drug. It is effective for partial seizures and infantile spasms [144]. However, the treatment with this drug carries a high risk of irreversible concentric visual field constriction, sometimes associated with a drop in visual acuity [34] and these visual field defects limit its use. Additional unpleasant side-effect of vigabatrin is gingival overgrowth [82]. Those effects may limit the use of GVG also as an anti-addictive drug.

Baclofen, a $GABA_B$ receptor agonist

Another type of anti-addictive action *via* GABAergic system involves $GABA_B$ receptor activation after the administration of baclofen, a drug, which is used in clinic for treatment of epilepsy, pain and uncontrolled hiccups. Baclofen dose-dependently inhibited reinforcing cocaine action, though produced no inhibition of natural rewarding stimuli in rats [110]. Preliminary clinical study suggested that potentially it could be applied for cocaine [69] and alcohol [1] anti-craving medication.

So-called substitutive therapies – agonistic pharmacotherapies

The therapeutic strategy consisting in treatment with the ligands competing with addiction-forming substances for their binding sites is usually called a substitutive or maintenance therapy. It has been treated suspiciously as "trying to get rid of a devil with a demon". However, usually such therapy does not require to treat a patient with an addictive drug itself (except for therapy of nicotine dependence by nicotine patches designed to supply nicotine by the route less harmful than smoking), since therapeutic agents used in substitutive therapy have different receptor binding characteristics in comparison with addiction-forming drugs. Their binding is typically slow but long-lasting, so subsequent administration of the abused drug does not cause towering stimulation of the reward system. Nevertheless, some of these drugs may have certain addictive potential.

Agonistic therapy of opiate addiction

Methadone and L-α-acetylmethadol (LAAM)

History of methadone has been recently presented by one of leader promoters of introduction of this substance into clinical practice, Marian Kreek [61]. The history of this drug started in 1963, when Vincent P. Dole established a research group focused on combating heroin abuse that was violently spreading at that time. They were alarmed by the increase in heroin overdose-related death rate and progressive spread of contagious diseases. Assuming a revolutionary, in those days, standpoint that drug abuse is not criminal behavior nor personality disorder but the brain disease accompanied by behavioral symptoms, the group undertook research to determine whether long-acting opioid receptor agonists, such as methadone, could be used in drug addiction treatment [32].

Over the next decades, many studies have accumulated which documented safety and efficacy of methadone pharmacotherapy, but fundamentalistic approach to methadone and resulting governmental regulations delayed its official introduction as an anti-addictive agent by 35 years. Only recently, in 1999, The National Institute of Health (NIH) published a report indicating unequivocally the advantages of methadone use in maintenance treatment of morphine addiction. The newest trials comprising large groups of patients have confirmed that methadone has beneficial effect not only during detoxification but also as a component of long-term maintenance treatment, decreasing illegal heroin use and reducing behaviors leading to spread of HIV infection [121]. Besides methadone, LAAM, another opioid receptor ligand, acting longer than methadone, has also been registered in the USA. Methadone and LAAM seem to be particularly effective in relapse prevention. Although these treatments are currently provided in special drug treatment settings, recent and ongoing research indicates that the physician's office may be an effective alternative site for these treatments [145]. It should be remembered, however, that both compounds have some abuse potential. Recent studies on intravenous administration of LAAM, in contrast to previous clinical reports, have demonstrated that LAAM

produces typical opioid effects of immediate onset when administered parenterally, which suggests that intravenous LAAM possesses greater abuse potential than previously believed [145].

Buprenorphine

Buprenorphine is a partial μ-opioid receptor agonist and κ-receptor antagonist. It does not need to be administered frequently since its action is very prolonged, which makes its use more convenient. Its effectiveness in drug addiction treatment was discovered at the end of the seventies [57, 80]. It is willingly taken by the patients since it has some euphoric effect but cessation of its administration does not evoke abstinence syndrome. Therapeutic efficacy of buprenorphine is comparable to that of methadone [120, 127]. Buprenorphine was shown to suppress cocaine self-administration in monkeys [81], but it did not reduce cocaine use by humans [120]. Nevertheless, recent studies have demonstrated that the combined treatment with disulfiram and buprenorphine decreases cocaine use by the addicted individuals [41]. Disulfiram administration before cocaine intake abolished euphoric action of the latter, evoking dysphoria and paranoid symptoms. In some countries, like in France, in which buprenorphine at high dosage became available in 1996, as a substitution treatment for heroin addicts, its use is less restricted than the use of methadone: methadone is only delivered in specialized centers while high dosage of buprenorphine can be prescribed by all general practitioners [7]. However, since its introduction numerous deaths were attributed to this drug. Intravenous injection of crushed tablets, concomitant intake of psychotropics (especially benzodiazepines and neuroleptics) and the high dosage of the buprenorphine formulation available in France appear the major risk factors for such fatalities [60].

Agonistic pharmacotherapy of addiction to psychostimulants

GBR12909 (Vanoxerine)

At the end of the eighties, dopamine uptake inhibitors, displaying tight and long-term binding to dopamine transporter, were noticed to, seemingly paradoxically, act as cocaine antagonists. This happens because the emergence of reinforcing effect requires repeated, phasic rather than tonic receptor activation. One of such compounds was 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl]}-4-[3-phenylpropyl]piperazine, known by a code name GBR12909, and recently named vanoxerine. Administered alone, vanoxerine caused only a slight increase in dopamine level in extracellular fluid in the brain tissue, but it strongly antagonized cocaine-induced rises in dopamine level and decreased cocaine binding to dopamine transporter [111, 114].

Reports that GBR12909 suppressed cocaine-evoked elevation of dopamine level in rodent mesolimbic system prompted researchers to carry out studies in primates. In baboons, GBR12909 infusion before amphetamine administration (1.5 mg/kg, *iv*) reduced dopamine surge by 74% [143], while in rhesus monkey, this compound at a dose of 1 mg/kg considerably decreased, and at 3 mg/kg eliminated, cocaine self-administration [142].

GBR12909 not only blocks direct cocaine effects but also shows "negative sensitization" toward cocaine. While pretreatment with a single dose of cocaine enhances locomotor effects and stereotypy induced by the next dose of cocaine or other dopamine transporter blockers given 24 h later, the cocaine pretreatment attenuates the stimulatory effect of GBR12909 [35].

All these data suggest that GBR12909, technically considered a cocaine substitute, exactly as methadone is a morphine substitute, is a promising agent for the treatment of cocaine dependence. Due to its high affinity for the dopamine transporter, GBR12909 acts much longer in the brain than cocaine does [133], and even a possibility is being considered to apply its decanoate in the treatment to obtain sustained release drug form. A study on the metabolism of GBR12909 in human liver microsomes concluded that CYP3A appears to be the major enzyme responsible for human GBR12909 biotransformation [19]. Potential activity of GBR12909 in cocaine addiction treatment has been reviewed by Rothman and Glowa [112].

Peripherally acting anti-addictive drugs: vaccines, enzymes, antibodies

This approach has the advantage of operating by means of an endogenous response that is independent of the central nervous system, thus circumventing the problem of neurotoxicity.

Psychoactive substances attack the brain, but to reach it they have to be transported there with

blood and cross the blood-brain barrier. Therefore, an alternative strategy of drug addiction treatment consists in the development of therapeutic agents capable of intercepting the molecules of a psychoactive substance before they reach their final target, and their neutralization during their journey to the brain. Such compounds, peripheral blockers of psychoactive drugs, have a number of potential advantages over other anti-addictive drugs: their design does not require knowledge of a detailed mechanism of drug action on neurons, they can efficiently neutralize psychoactive drugs with multiple targets, and can protect against peripheral effects of addiction-forming drugs, e.g. undesired circulatory and gastrointestinal reactions [155].

Design of peripheral blockers of addictive substances was based on natural defensive systems of the organism: enzymes and antibodies. Immunopharmacotherapy, wherein antibodies are used to neutralize the drug, offers a possible alternative to receptor-aimed pharmacotherapy. Anti-cocaine, anti--phencyclidine and anti-nicotine antibodies form complexes with the molecules of addictive substances. These complexes are too large to cross the blood-brain barrier. As a result, the drug remains in the periphery, where it is metabolized and excreted with urine. Another approach applies treatment with the substances that accelerate the metabolism of an addictive drug. The third strategy involves the stimulation of formation of antibodies that bind and destroy addictive drug molecules. Although high doses of the drug of abuse can break this defense line, peripheral antagonists can be a valuable supplementation of therapeutic programs aimed at preventing relapse and acute intoxication. Notwithstanding the fact that these drugs have not yet been introduced into clinical practice, preclinical results are encouraging, and phase one clinical trial of anti--cocaine vaccine seems to promise success [126]. Although most of the effort in production of vaccines against drugs of abuse concerned stimulants, there were also promising attempts to develop potent, long-lasting anti-morphine immune response for the treatment of morphine abuse [3] following observations from mid-70's [16].

Vaccines

Small molecules, such as cocaine molecules usually do not alarm the immunological system. However, cocaine molecules can be coupled with a protein carrier, stimulating immunological response. Mice vaccinated with such a complex produced specific anti-cocaine antibodies which bound the blood-borne drug molecules. Immunological response prevented cocaine entrance into the central nervous system of mice. It was a lasting effect, and periodical booster vaccination enabled to maintain a protective action for over a year [38]. Clinical trials of this vaccine are presently under way. The induced antibodies were demonstrated to bind tightly not only cocaine, but also its active metabolite, norcocaine, while they did not interact with inactive metabolites. The latter phenomenon prevents saturation of the antibodies with inactive metabolites, and facilitates their elimination [37]. In immunized rats injected with cocaine, the blood cocaine level was higher and its brain concentration was lower than in control rats, and 63% of the cocaine dose was bound in blood as early as 30 s after the injection. The immunized rats less willingly self-administered cocaine in comparison with the control animals. It may suggest that vaccinated patients will be less inclined to relapse in drug abuse. Obviously, a large cocaine dose will break the blockade, but therapeutic vaccines can be helpful for the patients who intend to quit drug abuse, since the medication blocks particularly the priming effect. Second generation anti-cocaine vaccines are now being developed in The Scripps Research Institute at La Jolla. Rats immunized with the cocaine immunoconjugate GND-keyhole limpet hemocyanin (KLH) or treated with the anti-cocaine antibody mAb GNC92H2 had dramatically suppressed responses to cocaine for a prolonged time. This suggested that newly developed immunopharmacotherapeutic agents have significant cocaine-blockade potential and therefore may offer an effective strategy for the treatment of cocaine abuse [18].

Although most attention was paid to peripheral cocaine blockage, therapeutic phencyclidine vaccines have also been developed. To remove this drug from the circulation (in the USA, numerous cases that required inpatient treatment following overdoses have been reported), monoclonal immunoglobulin G fragments were initially raised, capable of high-affinity phencyclidine binding (antiPCP-Fab) [94], and a full immunoglobulin protein (antiPCP--IgG) was later developed, which acted longer and bound phencyclidine more strongly. AntiPCP-FAB lowered phencyclidine level in the brain [136] and blocked behavioral effects of this drug and its derivatives [45, 135]. Later comparisons of antiPCP-

-Fab and antiPCP-IgG indicated that the latter much more strongly diminished brain phencyclidine level even if an animal received the drug in constant infusion for 4 weeks, and the half life of IgG-phencyclidine complex was estimated at more than 15 days [106]. Such antibodies are hoped to be used not only for detoxification in the cases of phencyclidine overdose, but also they can protect fetuses of women who abuse phencyclidine during pregnancy [78]. It is significant inasmuch as the animal studies demonstrated that phencyclidine and ketamine cross placental barrier and damage the fetus's brain [77].

Enzymes

Blood enzymes can metabolize cocaine and other psychoactive drugs, but they are not able to quickly neutralize such amounts of psychoactive drugs that are typically taken by addicts. When the incidence of acute cocaine poisoning was shown to be higher in the patients with low blood butyrylcholinesterase (BChE) level, this enzyme became a focus of further studies. They demonstrated that a rise in BChE activity could enhance efficacy of cocaine overdose treatment.

Carmona et al. [17] reported a very significant increase in cocaine metabolism and attenuation of its psychostimulatory action after elevation of BChE activity. BChE administration in rats at a dose causing 400-fold rise in blood enzyme activity shortened cocaine half life from more than 5 h to less than 5 min. Cocaine metabolic pathway was also changed, i.e. lesser amounts of the active metabolite were produced.

The studies have indicated that natural variability of BChE in humans can be responsible for diversified reactivity to cocaine. People with certain variants of the enzyme can respond to a standard cocaine dose with overdose symptoms. Very active variants of the enzyme have also been observed. Using genetic engineering methods, Oxana Lockridge's research group obtained very active mutant of BChE, designated as A328Y [153]. It appears that it can be used in intensive care of cocaine overdose [79].

Catalytic antibodies

Combination of two tactics of drug addiction treatment, i.e. those utilizing antibodies and enzymes, led to a design of catalytic antibodies, which bind to cocaine molecules (preventing their crossing the blood-brain barrier) and catalyze their degradation [83]. Cocaine molecule binding with the antibody changes the conformation of the former in such manner, that its hydrolysis to the systemically inert products, ecgonine methylester and benzoic acid, is accelerated. After hydrolysis, the inactive products split off and antibody is free to bind another cocaine molecule. Administration of anticocaine catalytic monoclonal antibody mAB 15A10 diminished consequences of cocaine overdose in rats, and decreased its self-administration. Further study with this antibody showed that when given 30 min before testing it reduced in a dose- and time--dependent manner cocaine self-administration across a wide cocaine dose range [6]. This suggests that catalytic antibodies that dramatically affect cocaine pharmacokinetics may be useful in the treatment of both cocaine overdose and cocaine addiction.

Other potential and currently used anti--addictive treatments

Pharmacotherapy of alcoholism

Problems associated with alcohol abuse, alcohol craving and alcoholism relapses have been recently detailed in an excellent review of Bieńkowski [15]. Although alcohol-related death rate is lower than that associated with nicotinism, the former exhibits higher criminalizing liability and produces much more drastic social effects. However, efficient pharmacotherapy of alcoholism begun to develop only in the last decade, since disulfiram "therapy", introduced after the World War II, can be considered neither efficient nor ethical. Two anti-alcoholic drugs: naltrexone and acamprosate have been successfully introduced into clinical practice.

Naltrexone

The discovery that naltrexone, an unspecific opiate receptor antagonist, effectively suppressed alcohol dependence was unexpected and very interesting. Naltrexone was registered as *ReVia* to be used as anti-alcoholic drug. Even though it is considered controversial by certain groups, particularly Alcoholics Anonymous [39], undoubtedly it effectively decreases alcohol craving, alcohol-evoked euphoria, alcohol consumption and relapse rate [87, 90, 116]. Good results in reduction of alcohol intake were obtained by combination of naltrexone and ondansetron [2].

Efficacy of opioid receptor antagonists in the treatment of alcohol addiction is associated with the fact that endogenous opioids play a key role in habit-forming action of alcohol. It has been hypothesized that one of alcohol effects may be β-endorphin release. Elevated alcohol consumption can be an attempt to compensate for the congenital deficits in opioid reward systems [51].

Naltrexone has successfully been used in the treatment of opiate addiction as well [24, 43], although recently its usefulness in this respect has been questioned [137]. An interesting approach was to combine naltrexone and buprenorphine, which was expected to enable fairly specific activation of κ-opioid receptors and evoke dysphoric effects. The studies comprising a small group of heroin abusers indicated that joint treatment with naltrexone and buprenorphine produced better results in comparison with naltrexone administration alone [113]. Moreover, preliminary experiments demonstrated beneficial naltrexone action in the patients dually addicted to cocaine and alcohol, the particularly treatment-resistant group [93].

It appears that naloxone, a compound similar to naltrexone, can also be applied in the therapy of amphetamine addiction, since naloxone blocked both amphetamine-induced locomotor effects and a rise in extracellular (dialyzable) dopamine level in the nucleus accumbens and striatum in the rats. However, corresponding effects of cocaine were not suppressed, which suggests that amphetamine addiction is connected with opioid system activity, while cocaine addiction is not controlled in such a way [119].

Naltrexone has also successfully been used in the reward system disturbances not related to drug addiction, such as anorexia and bulimia [75, 76]. On the other hand, an attempt to apply this drug in the treatment of nicotine addiction was unproductive [151].

Acamprosate

Acamprosate is a European drug, used particularly in France and registered as *Campral*. In terms of its chemical structure, it is a calcium N-acetylhomotaurinate, and can be considered a structural GABA analog. It probably interacts with GABA receptor but NMDA receptor is regarded as its main target [74]. This makes acamprosate an interesting agent, as both enhancement of GABAergic neurotransmission and antagonism of glutamatergic neurotransmission involving the NMDA receptor have been implicated in the mechanism of action of ethanol, and the results of substitution tests conducted with a number of GABA agonists and NMDA antagonists indicate that the discriminative stimulus effects of ethanol may involve both GABAergic and glutamatergic systems [123]. The recent data indicate an extremely weak antagonism of NMDA receptors by acamprosate, but show that the drug is able to modulate the expression of NMDA-receptor subunits in specific brain regions. This property is shared by acamprosate with the well-established NMDA antagonists memantine and MK-801, and may be of relevance for its therapeutic profile, especially considering the importance of the role of NMDA receptor plasticity in ethanol addiction [108]. Acamprosate action depends probably on a degree of receptor activity. Since alcohol also acts at GABA and NMDA receptors, and hyperactivity of NMDA receptor occurs in alcohol abstinence, both substances have common targets. Acamprosate properties most important for the mechanism of its therapeutic action include neuronal hyperactivity blockade and suppression of calcium influx into the cell. In animal models of craving, acamprosate was shown to reduce alcohol intake [125] and block elevated alcohol consumption during deprivation period [52].

Acamprosate has quite long been studied in clinical trials [67]. It is well-tolerated, it efficiently decreases relapse incidence during abstinence and its beneficial effects persist even after therapy discontinuation [118].

As mentioned above, naltrexone is a preferred compound for treatment of alcohol dependence in the USA, while acamprosate is more popular in Europe. Only recently the two treatments were directly compared. In this study naltrexone (50 mg/day) was compared with acamprosate (1665–1998 mg/day) on a group of 157 recently detoxified alcohol-dependent men with moderate dependence, and was proven superior to acamprosate in such parameters as the time to first relapse, number of patients abstinent for a period of one year (41% taking naloxone, 17% of receiving acamprosate), number of days with abstinence, number of days with heavy drinking, etc. [115].

Although both naltrexone and acamprosate, though with different efficacy, reduce relapse to alcohol use in recovering alcoholics, and both drugs given separately reduce intake of alcohol in

rats, in the animal model they have no synergistic effect, and hence the combined treatment with these drugs may not be any more effective than monotherapy [128].

Pharmacotherapy for nicotinism

Tobacco smoking, the presently most popular form of nicotinism, is a very strange addiction. It has been commonly accepted almost everywhere at least till the end of the last decade, so it had spread enormously. It seems that nicotinism is the most life-threatening habit among all drug addictions, as the rate of tobacco smoking-related deaths of cardiovascular disturbances and lung cancer 5-fold exceeds mortality due to consumption of alcohol, the second psychoactive substance legal in most parts of the world. What is more, one fifth of deaths affect involuntary passive smokers, nonsmokers exposed to tobacco smoke inhalation. In the USA, an estimated 400,000 people die of active tobacco smoking a year, and it is also a cause of 30% of deaths of cancer [92]. Nicotine addiction is acquired much easier that addiction to other psychoactive substances. Only minute percent of people who consume alcohol become alcoholics, while 40% of smokers are smoking addicts. This is connected probably with the fact that nicotine is used in an almost continuous manner, in contrast to other psychoactive substances which are usually taken on binges, with longer breaks.

Strength of nicotine addiction seems to be determined by the rate of nicotine metabolism in an organism. Populations with quicker metabolism, e.g. women and Afro-Americans, acquire stronger nicotine addiction, and are much more resistant to substitutive therapy (see below) [86].

Abstinence symptoms appear in smokers very quickly. Unpleasant reactions, accompanied by physiological changes occur several hours after the last cigarette. The typical withdrawal symptoms are aggressiveness, nervousness, excessive appetite, lack of concentration, mood depression, irresistible desire to smoke. All these symptoms disappear within a month, except for excessive appetite which leads to body weight gain observable in a week after smoking cessation and persisting usually for about 3 months. Craving attacks become rarer and less intense in time, but return over many months [146]. Suppression of these attacks and mitigation of nicotine abstinence symptoms are main goals of nicotinism treatment.

Until mid-nineties, the only effective anti-nicotinic pharmacotherapy was substitutive therapy with nicotine. It was applied transdermally using patches, orally as chewing gum or oral inhalators, and as nasal sprays [152].

In 1996, a letter to the editor of *American Journal of Psychiatry* reported that the administration of bupropion, an atypical antidepressant, dopamine and noradrenaline reuptake inhibitor, assisted smoking cessation in depressive patients [68]. This was a serendipitous observation, since antidepressant drugs are not considered efficacious medication in smoking cessation though it is believed that there exist undeniable interrelationships between depression and smoking habit (depression is more common in smokers than in non-smokers, smoking depressive patients more reluctantly cease smoking, mood depression is one of nicotine abstinence symptoms, and in 30% depressive patients depressive symptoms appear after smoking cessation) [23]. Further studies revealed that, besides bupropion, only nortriptyline proved to be an antidepressant drug assisting smoking cessation. The finding that almost none of antidepressant drugs facilitates smoking cessation suggests that the effectiveness of bupropion and nortriptyline is not associated with their antidepressant profile [11].

Introduction of bupropion into nicotinism treatment was the first efficient pharmacotherapy other than substitutive treatment. Even the first controlled trials of sustained-release bupropion yielded positive results [55], and further research indicated higher efficacy of bupropion than substitutive therapy with nicotine [47]. In May 1997, sustained-release bupropion (bupropion SR) was registered as *Zyban* and approved by the *Food and Drug Administration* in the USA for assistance in smoking cessation. Since than, in the USA bupropion has been used in more than 5 million patients, attempting to cease smoking [44]. Bupropion SR, administered at daily doses of 300 mg/kg for 7 or 9 weeks, significantly reduced relapse incidence in comparison not only with the patients receiving placebo but also with those treated with nicotine patches. Combined treatment with nicotine patches and bupropion yielded slightly better results that administration of bupropion alone, but the difference was not statistically significant. Bupropion therapy has another very valuable advantage, namely bupropion-assisted smoking cessation caused much less weight gain than that observed in remaining patients [54].

Bupropion efficacy remains unaffected by previous patient's depression episodes or alcoholism [48]. Bupropion is more effective than nicotine patches especially in women and Afro-Americans, who metabolize nicotine more rapidly [86]. Recent studies that examined long-term bupropion therapy used expressly for prevention of smoking relapse have revealed that in persons who stopped smoking with 7 weeks of treatment, sustained-release bupropion for 12 months significantly delayed smoking relapse and resulted in less weight gain [49].

As bupropion is an antidepressant, and many antidepressants are associated with sexual dysfunctions, its effect on sexual activity was studied in a large group of male depressed patients. It was found that bupropion produces much less sexual disturbances than a standard SSRI antidepressant, fluoxetine, and therefore bupropion SR may be an appropriate initial choice for the treatment of depression in patients concerned about sexual functioning [21]. This result suggests that the drug would not produce sexual disturbances also in the people who use it fighting nicotine addition.

In conclusion, at present, sustained-release bupropion is the first drug of choice in the therapy of nicotinism: it is effective and well-tolerated. Reduction of body weight gain during abstinence and the possibility to start the therapy even during regular smoking are additional advantages of this therapy.

WHAT CAN WE EXPECT IN THE 21ST CENTURY?

Future is obviously unpredictable, but some projections may be ventured. Even though all visions of the future, that I know, have one common feature: they never come true, prognostication is a nice job since it will surely render entertainment to those who will read the forecasts from before several decades and confront them with reality. Thus, what can we expect in the future with regard to psychotropic substances and their position in the society?

The first question is whether serious social and medical threats caused by drug addiction, which exist at present, will be overcome. It appears that success can be expected if we view pharmacotherapy of drug addiction strictly from medical standpoint. In fact, we already have basic knowledge of neuronal processes involved in rewarding and addictive actions. It is not full as yet, and new controversies, concerning neuronal mechanisms underlying these processes still continue to appear, but it is operant in the sense that it enables to select promising strategies. It is still not clear whether the most powerful help to combat drug addiction can be provided by therapeutic agents acting directly on the reward system, those affecting specific target systems for individual addiction-forming drugs or peripherally acting vaccines for these substances. Recently discovered CART peptides still await practical application. It is conceivable that the methods of genetic engineering will be applied to repair deficits of the reward system underlying the congenital increased vulnerability to drug addiction. However, it may happen that even slight improvement of already existing therapies will bring satisfactory results. Obviously, we cannot be a hundred per cent certain of success. At the end of 20th century, we seemed to get control over contagious diseases, such as smallpox, cholera or classic venereal diseases, and then we helplessly faced an attack of new viruses, such as HIV or Ebola, or entirely new contagious agents, prions. It cannot be excluded that new, difficult to handle addiction-forming substances will be discovered rather in chemical laboratories than in the institutes of tropical plant research, and the information on their availability and illicit use will spread through the internet.

It should be remembered that drug addiction is a disease but it is not only a medical problem, but also a social phenomenon, and its treatment requires psychological assistance. It appears that good programs assisting patients in recovery from drug abuse, such as Drug Abusers Anonymous, Focus on Family, or various so-called twelve-stage programs do exist, especially in the USA and Western Europe. However, there is some danger of nonsense competition between believers in pharmacotherapy and psychotherapy, mainly due to communication problems. Advocates of pharmacotherapy are often blamed for soulless or too liberal attitude toward the patients, and even accused of protecting drug abusers and providing them with the drugs in the guise of drug addiction treatment. Such objections are raised especially to heroin addiction treatment with methadone. As already mentioned, unfriendly attitude of psychotherapeutists, and particularly a fundamentalist approach of different, politically influential moralists delayed methadone introduction into practice for more than thirty years.

Moralizing approach to drug addiction, which assumes that drug abuser is a criminal or sinner deserving condemnation is costly and little effective unless we apply Singaporean variant calling for consistent hanging of all people who were found to possess even slight amounts of prohibited substances.

Rigorous penalization policy, however, is socially dangerous since it can give excessive power to police and opportunity for fraud (planting drugs). Moreover, it causes that drug abusers use drugs under stressful circumstances, which, as we know, enhance their rewarding action and strengthen addiction, predisposing to relapses (see [140]). Furthermore, penalized drug abuse incredibly increases crime rate, which was substantiated by the results of prohibition of alcoholic beverages in the USA by the terms of Eighteenth Amendment to the US Constitution. The law was abolished 13 years later by Twenty Third Amendment, but damages, particularly powerful underworld developed in that period, continued to exist.

The organized crime most strongly opposes combating drug addiction. The main cause of spread of drug abuse is an enormous profit from production, smuggling and dealing of prohibited substances. Undoubtedly, one of the reasons why prohibition was abolished in the USA was a decision that during Great Depression money should rather contribute to state funds than aid mobsters' pockets. Legalization of alcohol in the USA did not mean, however, lightening criminal law against drug abuse. Till the end of the eighties, criminal policy in the USA aimed to limit supply of drugs of abuse, so most actions were directed against drug dealers. In 1988, new, more stringent law was passed which intended to reduce demand by penalization of drug possession (Omnibus Drug Act). In consequence, the number of prisoners rose three times, with no effect on a decrease in drug use in recent years.

It appears that powerful criminal organizations deriving huge profit from dealing prohibited substances are highly interested in preserving application of police methods to solve drug addiction problem. They possess enough resources to organize campaigns seemingly aimed to fight drug abuse by sharpening penalization and questioning moral bases of pharmacotherapy, which actually causes soaring of drug prices. In Poland, dealers do not make profit out of peddling in schools cigarettes and vodka, frequently abused by students, but marihuana, heroin and amphetamine.

It is not certain, what will be the end of the controversy between fundamentalists, liberals and permissivists, who call for full legalization of all addiction-forming substances. So far expansion of fundamentalistic tendencies can be noted on a global scale, especially in Islamic world, but history of Christian Europe teaches us that periods of restrictive societies (the Middle Ages, Counter Reformation) were interspersed with periods of liberalization (the Renaissance, Enlightenment). Currently, liberal tendencies seem to prevail in European societies, and as democratization and access to information parallel technological progress, 21st century can be expected not to be a period of breaking the right to freedom and individual development of each society member. On the other hand, however, at the end of liberal 19th century, who could have foreseen sudden outbreak of Nazi and communistic totalitarian systems, which were unusually puritan with respect to the use of psychoactive substances and rewarding behaviors in general (though Soviet system made a splendid exemption for alcohol)?

Entirely opposite vision of the future forecasts that new, harmless pleasure-affording substances will be discovered, which will be widely used, and even employed to control a society. Perhaps it is worth to cite fragments of the lecture dealing with threats created by drugs of abuse and environmental pollution, delivered by Professor Danilewski at the international congress in Rome 107 years ago. He believed that different unnatural chemical substances introduced into the environment put health of protoplasm at risk, or, as we would say today, they cause damage at the molecular level. Views presented in this lecture are strikingly alive also today.

What natural property, able to satisfy significant protoplasm requirements can be found in the use of various stimulating agents, in the use of alcohol, tobacco, and abuse of morphine, cocaine, opium, ether, sulfone, etc.?

These substances are not indigenous to our living matter: they blunt our senses when our organism requires their assistance, and excite our nervous system when peace would be infinitely more useful and healthy. In all respects, civilization creates more and more artificial conditions, more and more foreign to our protoplasm.

What urges us to follow this way? If we examine main causes inciting all new inventions concerning directly nutrients and stimulating substances, we

will be able to easily distinguish a single motif, winding its way across a whole array of relevant facts. It is craving to satisfy a desire of bliss and enjoyment in the quickest and most frequent way. Unvarying pleasures tire us soon, we constantly try to relieve their monotony. Our nerves quickly become dull and we introduce more and more stimulating substances into our body to attain the same pleasure.

"Civilizational workshop" focuses every effort on contenting all requirements, with servilely readiness finding new agents serving constantly the same purpose.

Considering intense, constant and long-term introduction of alcoholic group into human body, it is surprising indeed that this molecular structure does not hitherto constitute any indispensable component of protoplasm of a majority of civilized world. However, there is no doubt that miserable organisms, existence of which is a shameful blame on the civilization, have alcohol-impregnated protoplasm. It should be kept in mind that those miserable beings are almost incapable of leading life similar to other people, unaided with constant alcohol supply.

It is misleading to believe that a man rarely encounters conditions similar do alcoholism. These are several habitual uses of the substances foreign to the organism, but common in some communities, against which a combat has already been initiated by knowledge and normal part of local communities: alcoholism, morphine and cocaine abuse, arsenicphagy, ether use, tobacco abuse, voluntary and involuntary eating of rotten food, etc.

Present technology supplements at times largely too long list of the substances, which people strenuously introduce into their matter. This exertion in technical research produces undoubtedly useful effects, but advantage of quite a number of new inventions was diminished by practical life, that attributed to them an abnormal character, and often harmful and detrimental for the organism.

Nevertheless, whoever can ensure that future technical chemical synthesis will not provide humanity with a hope to have a number of substances which can liberate mankind from plagues that preachers and philosophers have vainly attempted to eliminate. Lets imagine a time when several subcutaneous injections can cure one of a longstanding egoism, chronic conceit and bumptiousness, infidelity, finally of militarism and all other "isms".

Certainly, while awaiting such fortunate future, it would be sensible to possibly preserve purity and sensitivity of our protoplasm, protect it from the effect of alcohol, morphine, cocaine and so many other similar substances at least until that golden age arrives [131].

Hence, the idea of "a vaccine of happiness" is not anything new, even among scientists. Probably the most commonly known literary vision of a system making use of rewarding psychotropic substances is *Brave New World* written by Aldous Huxley in 1932. Inhabitants of this world were divided into classes, subjected to scientific conditioning, and additionally plied with a liquor of happiness, soma. With great intuition, this famous writer pictured all horrors of totalitarian, scientifically subjugated but at the same time happy and devoid of physical suffering society. This issue was explored further by many second-rate authors of science fiction works, although they were unable to make this message so overpowering.

Nevertheless, let's reflect – is the creation of such societies in future centuries only a pure fiction? Will an urge to consumption lead to a society of narconauts, if the world indeed becomes so rich that everyday problems with a struggle for bread and butter are eliminated? Is this vision better than the society, based on alcohol consumption (a model already approached by certain communities and social groups), a society of internauts and TV maniacs? Will living conditions on the overpopulated planet, so divergent from those to which our biology has adapted, and in which natural selection fully operated, force us to seek support from chemistry to change reactions of our nervous system?

With regard to the question whether the societies based on psychotropic drugs will be able to exist, my answer is negative. Civilization is driven by constant progress which is a result of unceasing intellectual effort of scientists and engineers. Experience teaches us that even though the artists can flourish while abusing drugs (e.g. Baudelaire, Witkacy and many others), and slight psychopathologies can even increase their creativity [71–73], and at least drug abuse does not disable them much, scientists and engineers cannot work with clouded mind. Admittedly, there are psychotropic substances which elevate capacity of scientist's brain, let us mention caffeine (and, reluctantly, nicotine and psychostimulants), but there are no active scientists among alcoholics and morphine abusers. Hitherto

known psychotropic drugs at doses exceedingly stimulating reward system inhibit cognitive system equally efficiently as downers, not to mention hallucinogens. The cultures which abuse such agents, notwithstanding even their high spiritual and artistic development, would be supplanted or controlled by intellectual technical cultures.

This remarks bring to mind a vision of humanity's end depicted by charismatic writer Herbert George Wells in *The Time Machine*, his first book published in 1895. At the close of its history, the mankind evolved into two races. Living under natural conditions on the surface of the earth, vegetarian, devoted to arts and happy during the day Eloi, fell into a panic of the night at dusk, when cannibal, living underground and highly technically developed Morlocks emerged to the surface. But no matter what anyone may say, Eloi were much more sympathetic than Morlocks...

REFERENCES

1. Addolorato G., Caputo F., Capristo E., Colombo G., Gessa G.L., Gasbarrini G.: Ability of baclofen in reducing alcohol craving and intake: II-Preliminary clinical evidence. Alcohol. Clin. Exp. Res., 2000, 24, 67–71.
2. Ait-Daoud N., Johnson B.A., Javors M., Roache J.D., Zanca N.A.: Combining ondansetron and naltrexone treats biological alcoholics: corroboration of self-reported drinking by serum carbohydrate deficient transferrin, a biomarker. Alcohol. Clin. Exp. Res., 2001, 25, 847–849.
3. Akbarzadeh A., Mehraby M., Zarbakhsh M., Farzaneh H.: Design and synthesis of a morphine-6-succinyl--bovine serum albumin hapten for vaccine development. Biotechnol. Appl. Biochem., 1999, 30, 139–146.
4. Antkiewicz-Michaluk L., Michaluk J., Romańska I., Vetulani J.: Cortical dihydropyridine binding sites and behavioral syndrome in morphine abstinent rat. Eur. J. Pharmacol., 1990, 180, 129–135.
5. Antkiewicz-Michaluk L., Michaluk J., Romańska I., Vetulani J.: Reduction of morphine dependence and potentiation of analgesia by chronic co-administration of nifedipine. Psychopharmacology, 1993, 111, 457––464.
6. Baird T.J., Deng S.X., Landry D.W., Winger G., Woods J.H.: Natural and artificial enzymes against cocaine. I. Monoclonal antibody 15A10 and the reinforcing effects of cocaine in rats. J. Pharmacol. Exp. Ther., 2000, 295, 1127–1134.
7. Barrau K., Thirion X., Micallef J., Chuniaud-Louche C., Bellemin B., San Marco J.L.: Comparison of methadone and high dosage buprenorphine users in French care centres. Addiction, 2001, 96, 1433–1441.
8. Baumann M.H., Rothman R.B., Pablo J.P., Mash D.C.: In vivo neurobiological effects of ibogaine and its O-desmethyl metabolite, 12-hydroxyibogamine (noribogaine), in rats. J. Pharmacol. Exp. Ther., 2001, 297, 531–539.
9. Beardsley P.M., Sokoloff P., Balster R.L., Schwartz J.C.: The D3R partial agonist, BP 897, attenuates the discriminative stimulus effects of cocaine and D-amphetamine and is not self-administered. Behav. Pharmacol., 2001, 12, 1–11.
10. Belozertseva I.V., Bespalov A.Yu.: Effects of NMDA receptor channel blockers, dizocilpine and memantine, on the development of opiate analgesic tolerance induced by repeated morphine exposures or social defeats in mice. Naunyn-Schmied. Arch. Pharmacol., 1998, 358, 270–274.
11. Berlin I.: Antidepressants in smoking cessation: is effectiveness independent of the antidepressant effect? Int. J. Neuropsychopharmacol., 2000, 3, S59.
12. Bespalov A.Y., Dravolina O.A., Zvartau E.E., Beardsley P.M., Balster R.L.: Effects of NMDA receptor antagonists on cocaine-conditioned motor activity in rats. Eur. J. Pharmacol., 2000, 390, 303–311.
13. Bespalov A.Y., Zvartau E.E., Balster R.L., Beardsley P.M.: Effects of N-methyl-D-aspartate receptor antagonists on reinstatement of cocaine-seeking behavior by priming injections of cocaine or exposures to cocaine-associated cues in rats. Behav. Pharmacol., 2000, 11, 37–44.
14. Biała G., Langwiński R.: Effects of calcium channel antagonists on the reinforcing properties of morphine, ethanol and cocaine as measured by place conditioning. J. Physiol. Pharmacol., 1996, 47, 497–502.
15. Bieńkowski P.: Alcohol craving and heavy drinking relapses – advances in experimental psychopharmacotherapy (Polish). Farmakoter. Psychiatr. Neurol., 1999, 3, 82–96.
16. Bonese K.F., Wainer B.H., Fitch F.W., Rothberg R.M., Schuster C.R.: Changes in heroin self-administration by a rhesus monkey after morphine immunisation. Nature, 1974, 252, 708–710.
17. Carmona G.N., Schindler C.W., Shoaib M., Jufer R., Cone E.J., Goldberg S.R., Greig N.H., Yu Q.S., Gorelick D.A.: Attenuation of cocaine-induced locomotor activity by butyrylcholinesterase. Exp. Clin. Psychopharmacol., 1998, 6, 274–279.
18. Carrera M.R.A., Ashley J.A., Wirsching P., Koob G.F., Janda K.D.: A second-generation vaccine protects against the psychoactive effects of cocaine. Proc. Nat. Acad. Sci. USA, 2001, 98, 1988–1992.
19. Cherstniakova S.A., Bi D., Fuller D.R., Mojsiak J.Z., Collins J.M., Cantilena L.R.: Metabolism of vanoxerine, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR12909). Drug Metab. Dispos., 2001, 29, 1216–1220.
20. Childress A.R.: Dopamine receptor partial agonists could address the duality of cocaine craving. Trends Pharmacol. Sci., 2000, 21, 6–9.

21. Coleman C.C., King B.R., Bolden-Watson C., Book M.J., Segraves R.T., Richard N., Ascher J., Batey S., Jamerson B., Metz A.: A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin. Ther., 2001, 23, 1040–1058.
22. Collins E.D., Ward A.S., McDowell D.M., Foltin R.W., Fischman M.W.: The effects of memantine on the subjective, reinforcing and cardiovascular effects of cocaine in humans. Behav. Pharmacol., 1998, 9, 587–598.
23. Covey L.S., Glassman A.H., Stetner F.: Major depression following smoking cessation. Amer. J. Psychiat., 1997, 154, 263–265.
24. Crabtree B.L.: Review of naltrexone, a long-acting opiate antagonist. Clin. Pharmacol., 1984, 3, 273–280.
25. Cramer C.M., Gardell L.R., Boedeker K.L., Harris J.R., Hubbell C.L., Reid L.D.: Isradipine combined with naltrexone persistently reduces the reward-relevant effects of cocaine and alcohol. Pharmacol. Biochem. Behav., 1998, 60, 345–356.
26. Criswell H.E., Mueller R.A., Breese G.R.: Long-term D1 dopamine receptor sensitization in neonatal 5-OH-DA lesioned rats is blocked by an NMDA antagonist. Brain Res., 1990, 512, 284–290.
27. Danysz W., Parsons A.C.G.: Glycine and N-methyl--D-aspartate receptors: physiological significance and possible therapeutic applications. Pharmacol. Rev., 1998, 50, 597–664.
28. Dewey S.L., Brodie J.D., Gerasimov M., Horan B., Gardner E.L., Ashby C.R. Jr.: A pharmacologic strategy for the treatment of nicotine addiction. Synapse, 1999, 31, 76–86.
29. Dewey S.L., Morgan A.E., Ashby C.R. Jr., Horan B., Kushner S.A., Logan J., Volkow N.D., Fowler J.S., Gardner E.L., Brodie J.D.: A novel strategy for the treatment of cocaine addiction. Synapse, 1998, 30, 119–129.
30. Di Chiara G.: A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J. Psychopharmacol., 1998, 12, 54–67.
31. Dogrul A., Yesilyurt O., Deniz G., Isimer A.: Analgesic effects of amlodipine and its interaction with morphine and ketorolac-induced analgesia. Gen. Pharmacol., 1997, 29, 839–845.
32. Dole V.P., Nyswander M.E.: Medical treatment for diacetyl-morphine (heroin) addiction. JAMA, 1965, 193, 80–84.
33. Druhan J.P., Jakob A., Stewart J.: The development of behavioral sensitization to apomorphine is blocked by MK-801. Eur. J. Pharmacol., 1993, 243, 73–77.
34. Editorial: Visual field constriction on vigabatrin. Prescrire Int., 2000, 9, 210–211.
35. Elmer G.I., Brockington A., Gorelick D.A., Carrol F.I., Rice K.C., Matecka D., Goldberg S.R., Rothman R.B.: Cocaine cross-sensitization to dopamine uptake inhibitors: unique effects of GBR12909. Pharmacol. Biochem. Behav., 1996, 53, 911–918.
36. Forman R.F., Bovasso G., Woody G.: Staff beliefs about addiction treatment. J. Subst. Abuse Treat., 2001, 23, 1–9.
37. Fox B.S.: Development of a therapeutic vaccine for the treatment of cocaine addiction. Drug Alcohol Dependence, 1997, 48, 153–158.
38. Fox B.S., Kantak K.M., Edwards M.A., Black K.M., Bollinger B.K., Botka A.J., French T.L., Thompson T.L., Schad V.C., Greenstein J.L., Gefter M.L., Exley M.A., Swain P.A., Briner T.J.: Efficacy of a therapeutic cocaine vaccine in rodent models. Nat. Med., 1996, 2, 1129–1132.
39. Freed P.E., York L.N.: Naltrexone: a controversial therapy for alcohol dependence. J. Psychosoc. Nurs. Ment. Health. Serv., 1997, 35, 24–28.
40. Fuller R.K., Hiller-Sturmhofel S.: Alcoholism treatment in the United States. An overview. Alcohol Res. Health, 1999, 23, 69–77.
41. George T.P., Chawarski M.C., Pakes J., Carroll K.M., Kosten T.R., Schottenfeld R.S.: Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. Biol. Psychiat., 2000, 47, 1080–1086.
42. Gerasimov M.R., Ashby C.R. Jr., Gardner E.L., Mills M.J., Brodie J.D., Dewey S.L.: Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. Synapse, 1999, 34, 11–19.
43. Ginzburg H.M., Glass W.J.: The role of the National Institute on Drug Abuse in the development of naltrexone. J. Clin. Psychiat., 1984, 45, 4–6.
44. Glover E.D., Tucker V.L., Winter P.D.O.B.: Efficacy and tolerability of bupropion sustained-release for smoking cessation: a review of pivotal studies. Int. J. Neuropsychopharmacol., 2000, 3, S326.
45. Hardin J.S., Wessinger W.D., Proksch J.W., Owens S.M.: Pharmacodynamics of a monoclonal antiphencyclidine Fab with broad selectivity for phencyclidine-like drugs. J. Pharmacol. Exp. Ther., 1998, 285, 1113–1122.
46. Hasegawa A.E., Zacny J.P.: The influence of three L-type calcium channel blockers on morphine effects in healthy volunteers. Anesth. Analg., 1997, 85, 633––638.
47. Haustein K.O.: Pharmacotherapy of nicotine dependence. Int. J. Clin. Pharmacol. Ther., 2000, 38, 273–290.
48. Hayford K.E., Patten C.A., Rummans T.A., Schroeder D.R., Offord K.P., Croghan I.T., Glover E.D., Sachs D.P., Hurt R.D.: Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. Brit. J. Psychiat., 1999, 174, 173–178.
49. Hays J.T., Hurt R.D., Rigotti N.A., Niaura R., Gonzales D., Durcan M.J., Sachs D.P., Wolter T.D., Buist A.S., Johnston J.A., White J.D.: Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. Ann. Intern. Med., 2001, 135, 423–433.

50. Herning R.I., Guo X., Lange W.R.: Nimodipine improves information processing in substance abusers. Ann. NY Acad. Sci., 1995, 765, 152–159.
51. Herz A.: Endogenous opioid systems and alcohol addiction. Psychopharmacology, 1997, 129, 99–111.
52. Heyser C.J., Schulteis G., Durbin P., Koob G.F.: Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. Neuropsychopharmacology, 1998, 18, 125–133.
53. Hollerman J.R., Schultz W.: Dopamine neurons report an error in the temporal prediction of reward during learning. Nat. Neurosci., 1998, 1, 304–309.
54. Holm K.J., Spencer C.M.: Bupropion: a review of its use in the management of smoking cessation. Drugs, 2000, 59, 1007–1024.
55. Hurt R.D., Sachs D.P., Glover E.D., Offord K.P., Johnston J.A., Dale L.C., Khayrallah M.A., Schroeder D.R., Glover P.N., Sullivan C.R., Croghan I.T., Sullivan P.M.: A comparison of sustained-release bupropion and placebo for smoking cessation. N. Engl. J. Med., 1997, 337, 1195–1202.
56. Hyytia P., Backstrom P., Liljequist S.: Site-specific NMDA receptor antagonists produce differential effects on cocaine self-administration in rats. Eur. J. Pharmacol., 1999, 378, 9–16.
57. Jasinski D.R., Pevnick J.S., Griffith J.D.: Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch. Gen. Psychiat., 1978, 35, 501–516.
58. Jeziorski M., White F.J., Wolf M.E.: MK-801 prevents the development of behavioral sensitization during repeated morphine administration. Synapse, 1994, 16, 137–147.
59. Karler R., Calder L.D., Chaudhry I.A., Turkanis S.A.: Blockade of 'reverse tolerance' to cocaine and amphetamine by MK-801. Life Sci., 1989, 45, 599–606.
60. Kintz P.: Deaths involving buprenorphine: a compendium of French cases. Forensic Sci. Int., 2001, 121, 65–69.
61. Kreek M.J.: Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine Ann. NY Acad. Sci., 2000, 909, 186–216.
62. Kuzmin A., Martellotta M.C., Fratta W., Gessa G.L., Zvartau E.: Effect of isradipine, a dihydropyridine-calcium antagonist on i.v. self-administration of morphine in rats. Life Sci., 1996, 59, 159–164.
63. Kuzmin A.V., Patkina N.A., Zvartau E.E.: Analgesic and reinforcing effects of morphine in mice. Influence of Bay K-8644 and nimodipine. Brain Res., 1994, 652, 1–8.
64. Kuzmin A., Semenova S., Ramsey N.F., Zvartau E.E., Van Ree J.M.: Modulation of cocaine intravenous self-administration in drug-naive animals by dihydropyridine Ca2+ channel modulators. Eur. J. Pharmacol., 1996, 295, 19–25.
65. Kuzmin A., Zvartau E., Gessa G.L., Martellotta M.C., Fratta W.: Calcium antagonists isradipine and nimodipine suppress cocaine and morphine intravenous self-administration in drug-naive mice. Pharmacol. Biochem. Behav., 1992, 41, 497–500.
66. Leal M.B., Emanuelli T., Porciuncula L.D., Souza D.O., Elisabetsky E.: Ibogaine alters synaptosomal and glial glutamate release and uptake. NeuroReport, 2001, 12, 263–267.
67. Lhuintre J.P., Moore N., Tran G., Steru L., Langrenon S., Daoust M., Parot P., Ladure P., Libert C., Boismare F. et al.: Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol Alcoholism, 1990, 25, 613–622.
68. Lief H.I.: Bupropion treatment of depression to assist smoking cessation. Amer. J. Psychiat., 1996 153, 442.
69. Ling W., Shoptaw S., Majewska D.: Baclofen as a cocaine anti-craving medication: a preliminary clinical study. Neuropsychopharmacology, 1998, 18, 403–404.
70. Lotsof H.S.: Ibogaine in the treatment of chemical depencency disorders: clinical perspectives. Bull. MAPS, 1995, 5, 16–27.
71. Ludwig A.M.: Alcohol input and creative output. Brit. J. Addict., 1990, 85, 953–963.
72. Ludwig A.M.: Creative achievement and psychopathology: comparison among professions. Amer. J. Psychother., 1992, 46, 330–356.
73. Ludwig A.M.: Mental illness and creative activity in female writers. Amer. J. Psychiat., 1994, 151, 1650––1656.
74. Madamba S.G., Schweitzer P., Zieglgänsberger W., Siggins G.R.: Acamprosate (calcium acetylhomotaurinate) enhances the N-methyl-D-aspartate component of excitatory neurotransmission in rat hippocampal CA1 neurons in vitro. Alcohol. Clin. Exp. Res., 1996, 20, 651–658.
75. Marrazzi M.A., Bacon J.P., Kinzie J., Luby E.D.: Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. Int. Clin. Psychopharmacol., 1995, 10, 163–172.
76. Marrazzi M.A., Kinzie J., Luby E.D.: A detailed longitudinal analysis on the use of naltrexone in the treatment of bulimia. Int. Clin. Psychopharmacol., 1995, 10, 173–176.
77. Mathias R.: Ketamine, PCP, and alcohol trigger widespread cell death in the brains of developing rats. NIDA Notes, 2000, 15, 6–7.
78. Mathias R.: Antibody may treat PCP overdose and abuse, also block prenatal harm. NIDA Notes, 2000, 15, 8–9.
79. Mattes C.E., Belendiuk G.W., Lynch T.J., Brady R.O., Dretchen K.L.: Butyrylcholinesterase: an enzyme antidote for cocaine intoxication. Addict. Biol., 1998, 3, 171–188.
80. Mello N.K., Mendelson J.H.: Buprenorphine suppresses heroin use by heroin addicts. Science, 1980, 207, 657–659.

81. Mello N.K., Mendelson J.H., Bree M.P., Lukas S.E.: Buprenorphine suppresses cocaine self-administration by rhesus monkeys. Science, 1989, 245, 859–862.
82. Mesa F.L., Lopez C., Gonzalez M.A., Del-Moral R., OValle F.J.: Clinical and histopathological description of a new case of vigabatrin-induced gingival overgrowth. Med. Oral, 2000, 5, 133–137.
83. Mets B., Winger G., Cabrera C., Seo S., Jamdar S., Yang G., Zhao K., Briscoe R.J., Almonte R., Woods J.H., Landry D.W.: A catalytic antibody against cocaine prevents cocaine's reinforcing and toxic effects in rats. Proc. Nat. Acad. Sci. USA, 1998, 95, 10176–10181.
84. Michaluk J., Karolewicz B., Antkiewicz-Michaluk L., Vetulani J.: Effects of various Ca2+ channel antagonists on morphine analgesia, tolerance and dependence, and on blood pressure in the rat. Eur. J. Pharmacol., 1998, 352, 189–197.
85. Muntaner C., Kumor K.M., Nagoshi C., Jaffe J.H.: Effects of nifedipine pretreatment on subjective and cardiovascular responses to intravenous cocaine in humans. Psychopharmacology, 1991, 105, 37–41.
86. Nichols M.R.: The use of bupropion hydrochloride for smoking cessation therapy. Clin. Excell. Nurse Pract., 1999, 3, 317–322.
87. O'Brien C.P., Volpicelli L.A., Volpicelli J.R.: Naltrexone in the treatment of alcoholism: a clinical review. Alcohol, 1996, 13, 35–39.
88. O'Hearn E., Long D.B., Molliver M.E.: Ibogaine induces glial activation in parasagittal zones of the cerebellum. NeuroReport, 1993, 4, 299–302.
89. O'Hearn E., Molliver M.E.: Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline. Neuroscience, 1993, 55, 303–310.
90. O'Malley S.S.: Opioid antagonists in the treatment of alcohol dependence: clinical efficacy and prevention of relapse. Alcohol Alcoholism Suppl., 1996, 1, 77–81.
91. Ohmori T., Abekawa T., Muraki A., Koyama T.: Competitive and noncompetitive NMDA antagonists block sensitization to methamphetamine. Pharmacol. Biochem. Behav., 1994, 48, 587–591.
92. Okuyemi K.S., Ahluwalia J.S., Harris K.J.: Pharmacotherapy of smoking cessation. Arch. Fam. Med., 2000, 9, 270–281.
93. Oslin D.W., Pettinati H.M., Volpicelli J.R., Wolf A.L., Kampman K.M., O'Brien C.P.: The effects of naltrexone on alcohol and cocaine use in dually addicted patients. J. Subst. Abuse Treat., 1999, 16, 163–167.
94. Owens S.M., Mayersohn M.: Modulation of phencyclidine (PCP) pharmacokinetics with PCP-specific Fab fragments. NIDA Res. Monogr., 1986, 64, 112–126.
95. Parsons C.G., Danysz W., Quack G.: Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist – a review of preclinical data. Neuropharmacology, 1999, 38, 735–767.
96. Pereira I.T., Prado W.A., Dos Reis M.P.: Enhancement of the epidural morphine-induced analgesia by systemic nifedipine. Pain, 1993, 53, 341–345.
97. Piasecki J., Koros E., Dyr W., Kostowski W., Danysz W., Bienkowski P.: Ethanol-reinforced behaviour in the rat: effects of uncompetitive NMDA receptor antagonist, memantine. Eur. J. Pharmacol., 1998, 354, 135–143.
98. Pilla M., Perachon S., Sautel F., Garrido F., Mann A., Wermuth C.G., Schwartz J.C., Everitt B.J., Sokoloff P.: Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. Nature, 1999, 400, 371–375.
99. Popik P.: Addiction suppression by NMDA receptor antagonists: history of discovery and mechanism of action of ibogaine (Polish). 1997, http://www.if-pan.krakow.pl/~popikp/ibogaina/ibogaine_pl.html#iboga.
100. Popik P., Kolasiewicz W.: Mesolimbic NMDA receptors are implicated in the expression of conditioned morphine reward. Naunyn-Schmied. Arch. Pharmacol., 1999, 359, 288–294.
101. Popik P., Kozela E.: Clinically available NMDA antagonist, memantine, attenuates tolerance to analgesic effects of morphine in a mouse tail flick test. Pol. J. Pharmacol., 1999, 51, 223–231.
102. Popik P., Kozela E., Danysz W.: Clinically available NMDA receptor antagonists memantine and dextromethorphan reverse existing tolerance to the antinociceptive effects of morphine in mice. Naunyn-Schmied. Arch. Pharmacol., 2000, 361, 425–432.
103. Popik P., Layer R.T., Skolnick P.: 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. Pharmacol. Rev., 1996, 53, 791–798.
104. Popik P., Skolnick P.: The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence. Pharmacol. Biochem. Behav., 1996, 53, 791–798.
105. Preti A.: BP-897 Bioprojet. Curr. Opin. Investig. Drugs, 2000, 1, 110–115.
106. Proksch J.W., Gentry W.B., Owens S.M.: Anti-phencyclidine monoclonal antibodies provide long-term reductions in brain phencyclidine concentrations during chronic phencyclidine administration in rats. J. Pharmacol. Exp. Ther., 2000, 292, 831–837.
107. Pudiak C.M., Bozarth M.A.: L-NAME and MK-801 attenuate sensitization to the locomotor-stimulating effect of cocaine. Life Sci., 1993, 53, 1517–1524.
108. Rammes G., Mahal B., Putzke J., Parsons C., Spielmanns P., Pestel E., Spanagel R., Zieglgansberger W., Schadrack J.: The anti-craving compound acamprosate acts as a weak NMDA-receptor antagonist, but modulates NMDA-receptor subunit expression similar to memantine and MK-801. Neuropharmacology, 2001, 40, 749–760.
109. Redgrave P., Prescott T.J., Gurney K.: Is the short-latency dopamine response too short to signal reward error? Trends Neurosci., 1999, 22, 146–151.
110. Roberts D.C., Andrews M.M., Vickers G.J.: Baclofen attenuates the reinforcing effects of cocaine in rats. Neuropsychopharmacology, 1996, 15, 417–423.

111. Rothman R.B., Mele A., Reid A.A., Akunne H.C., Greig N., Thurkauf A., de Costa B.R., Rice K.C., Pert A.: GBR12909 antagonizes the ability of cocaine to elevate extracellular levels of dopamine. Pharmacol. Biochem. Behav., 1991, 40 387–397.
112. Rothman R.B., Glowa J.R.: A review of the effects of dopaminergic agents on humans, animals, and drug-seeking behavior, and its implications for medication development. Focus on GBR 12909. Mol. Neurobiol., 1995, 11, 1–19.
113. Rothman R.B., Gorelick D.A., Heishman S.J., Eichmiller P.R., Hill B.H., Norbeck J., Liberto J.G.: An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. J. Subst. Abuse Treat., 2000, 18, 277–281.
114. Rothman R.B., Mele A., Reid A.A., Akunne H., Greig N., Thurkauf A., Rice K.C., Pert A.: Tight binding dopamine reuptake inhibitors as cocaine antagonists. A strategy for drug development. FEBS Lett., 1989, 257, 341–344.
115. Rubio G., Jimenez-Arriero M.A., Ponce G., Palomo T.: Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol Alcoholism, 2001, 36, 419–425.
116. Rueff B.: Évaluation des traitements médicamenteux de l'alcoolodépendance psychique primaire. Rev. Prat., 1999, 49, 400–402.
117. Santillan R., Hurle M.A., Armijo J.A., de los Mozos R., Florez J.: Nimodipine-enhanced opiate analgesia in cancer patients requiring morphine dose escalation: a double-blind, placebo-controlled study. Pain, 1998, 76, 17–26.
118. Sass H., Soyka M., Mann K., Zieglgansberger W.: Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch. Gen. Psychiat., 1996, 53, 673–680.
119. Schad C.A., Justice J.B. Jr., Holtzman S.G.: Naloxone reduces the neurochemical and behavioral effects of amphetamine but not those of cocaine. Eur. J. Pharmacol., 1995, 275, 9–16.
120. Schottenfeld R.S., Pakes J.R., Oliveto A., Ziedonis D., Kosten T.R.: Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch. Gen. Psychiat., 1997, 54, 713–720.
121. Sees K.L., Delucchi K.L., Masson C., Rosen A., Clark H.W., Robillard H., Banys P., Hall S.M.: Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. JAMA, 2000, 283, 1303–1310.
122. Semenova S., Danysz W., Bespalov A.: Low-affinity NMDA receptor channel blockers inhibit acquisition of intravenous morphine self-administration in naive mice. Eur. J. Pharmacol., 1999, 378, 1–8.
123. Shelton K.L.K., Balster R.L.R.: Ethanol drug discrimination in rats: substitution with GABA agonists and NMDA antagonists. Behav. Pharmacol., 1994, 5, 441–451.
124. Silverstone P.H., Attenburrow M.J., Robson P.: The calcium channel antagonist nifedipine causes confusion when used to treat opiate withdrawal in morphine-dependent patients. Int. Clin. Psychopharmacol., 1992, 7, 87–90.
125. Spanagel R., Zieglgänsberger W.: Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends Pharmacol. Sci., 1997, 18, 54–59.
126. Sparenborg S., Vocci F., Zukin S.: Peripheral cocaine-blocking agents: New medications for cocaine dependence. Drug Alcohol Dependence, 1997, 48, 149–151.
127. Strain E.C., Stitzer M.L., Liebson I.A., Bigelow G.E.: Comparison of buprenorphine and methadone in the treatment of opioid dependence. Amer. J. Psychiat., 1994, 151, 1025–1030.
128. Stromberg M.F., Mackler S.A., Volpicelli J.R., O'Brien C.P.: Effect of acamprosate and naltrexone, alone or in combination, on ethanol consumption. Alcohol, 2001, 23, 109–116.
129. Suh H.W., Song D.K., Choi S.R., Huh S.O., Kim Y.H.: Effects of intrathecal injection of nimodipine, omega-conotoxin GVIA, calmidazolium, and KN-62 on the antinociception induced by cold water swimming stress in the mouse. Brain Res., 1997, 767, 144–147.
130. Szumlinski K.K., Haskew R.E., Balogun M.Y., Maisonneuve I.M., Glick S.D.L.: Iboga compounds reverse the behavioural disinhibiting and corticosterone effects of acute methamphetamine: Implications for their antiaddictive properties. Pharmacol. Biochem. Behav., 2001, 69, 485–491.
131. Szymanowski Z.: Protoplasm. Lecture by Prof. Danilewski at the International Congress of Physicians in Rome in 1894. Wszechświat, 1895, 14, 263–265.
132. Trujillo K.A., Akil H.: Excitatory amino acids and drugs of abuse: a role for N-methyl-D-aspartate receptors in drug tolerance, sensitization and physical dependence. Drug Alcohol Dependence, 1995, 38, 139–154.
133. Tsukada H., Harada N., Nishiyama S., Ohba H., Kakiuchi T.: Dose-response and duration effects of acute administrations of cocaine and GBR12909 on dopamine synthesis and transporter in the conscious monkey brain: PET studies combined with microdialysis. Brain Res., 2000, 860, 141–148.
134. Tzchentke T.M., Schmidt W.J.: Effects of the non-competitive NMDA-receptor antagonist memantine on morphine- and cocaine-induced potentiation of lateral hypothalamic brain stimulation reward. Psychopharmacology, 2000, 149, 225–234.
135. Valentine J.L., Mayersohn M., Wessinger W.D., Arnold L.W., Owens S.M.: Antiphencyclidine monoclonal Fab fragments reverse phencyclidine-induced behavioral effects and ataxia in rats. J. Pharmacol. Exp. Ther., 1996, 278, 709–716.
136. Valentine J.L., Owens S.M.: Antiphencyclidine monoclonal antibody therapy significantly changes phencyclidine concentrations in brain and other tissues in rats. J. Pharmacol. Exp. Ther., 1996, 278, 717–724.

137. van Brussel G.H.: Limited role of naltrexone in the treatment of opiate addiction. Ned. Tijdschr. Geneeskd., 2001, 145, 1452–1456.
138. Vetulani J.: Calcium and voltage-dependent calcium channels (Polish). Kosmos, 1997, 46, 491–505.
139. Vetulani J.: Drug addiction. Part I. Psychoactive substances in the past and presence. Pol. J. Pharmacol., 2001, 53, 201–214.
140. Vetulani J.: Drug addiction. Part II. Neurobiology of addiction. Review. Pol. J. Pharmacol., 2001, 53, 303––317.
141. Vigabatrin. GVG, MDL 71754, RMI 71754, Sabril, Sabrilex, gamma-vinyl-GABA. Drugs R.D., 1999, 2, 393–396.
142. Villemagne V.L., Rothman R.B., Yokoi F., Rice K.C., Matecka D., Dannals R.F., Wong D.F.: Doses of GBR-12909 that suppress cocaine self-administration in non-human primates substantially occupy dopamine transporters as measured by [11C] WIN35,428 PET scans. Synapse, 1999, 32, 44–50.
143. Villemagne V.L., Wong D.F., Yokoi F., Stephane M., Rice K.C., Matecka D., Clough D.J., Dannals R.F., Rothman R.B.: GBR12909 attenuates amphetamine--induced striatal dopamine release as measured by [^{11}C]raclopride continuous infusion PET scans. Synapse, 1999, 33, 268–273.
144. Wallace S.J.: Newer antiepileptic drugs: advantages and disadvantages. Brain Dev., 2001, 23, 277–283.
145. Walsh S.L., Johnson R.E., Cone E.J., Bigelow G.E.: Intravenous and oral l-alpha-acetylmethadol: pharmacodynamics and pharmacokinetics in humans. J. Pharmacol. Exp. Ther., 1998, 285, 71–82.
146. West R.J.: Signs and symptoms during the acute phase of smoking cessation. Int. J. Neuropsychopharmacol., 2000, 3, Suppl. 1, S59.
147. Wicke K., Garcia-Ladona J.: The dopamine D3 receptor partial agonist, BP 897, is an antagonist at human dopamine D3 receptors and at rat somatodendritic dopamine D3 receptors. Eur. J. Pharmacol., 2001, 424, 85–90.
148. Włodarski A.: Without crash, without rush (Polish). Gazeta Wyborcza, 1999, nr 170.
149. Wolf M.E., Jeziorski M.: Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than transiently masks the development of behavioral sensitization. Brain Res., 1993, 613, 291–294.
150. Wolf M.E., Khansa M.R.: Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. Brain Res., 1991, 562, 164–168.
151. Wong G.Y., Wolter T.D., Croghan G.A., Croghan I.T., Offord K.P., Hurt R.D.: randomized trial of naltrexone for smoking cessation. Addiction, 1999, 94, 1227––1237.
152. Wongwiwatthananukit S., Jack H.M., Popovich N.G.: Smoking cessation. Part 2. Pharmacologic approaches. J. Amer. Pharm. Assoc. (Washington), 1998, 38, 339––353.
153. Xie W., Altimirano C.V., Bartels C.F., Speirs R.J., Cashman J.R., Lockridge O.: An improved cocaine hydrolase: The A328Y mutant of human butyrylcholinesterase is 4-fold more efficient. Mol. Pharmacol., 1999, 55, 83–91.
154. Zarauza R., Saez-Fernandez A.N., Iribarren M.J., Carrascosa F., Adame M., Fidalgo I., Monedero P.: A comparative study with oral nifedipine, intravenous nimodipine, and magnesium sulfate in postoperative analgesia. Anesth. Analg., 2000, 91, 938–943.
155. Zikler P.: Blood-borne medications could intercept drugs before they reach the brain. NIDA Notes, 2000, 14, 8–11.

Received: October 3, 2001; in revised form: October 17, 2001.