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NEUROPSYCHOPHARMACOLOGY

Pharmacotherapy of substance use disorders in the neuroscience-based nomenclature (NbN)

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Summary In the field of substance use disorders (SUDs), medications are frequently labeled according to their main symptomatic effect (e.g., ''anticraving drugs'') or according to imprecise and sometimes old concepts related to treatment strategies (e.g., ''replacement therapies'', ''antabuse drugs'', or ''substitution treatments''). By contrast, the neuroscience-based nomenclature (NbN) offers a clearer and more consistent rationale, according to which the main element of classification is based on the pharmacological mode of action of the medication. This review aims to display the different approved treatments used in SUDs, and to discuss the pros and cons of using this new conceptual framework in the field of addiction. According to the NbN classification, medications approved in the different SUDs can be classified in the different following categories: 1) nicotinic drugs; 2) GABAergic drugs; 3) opioid drugs; and 4) others. More specifically, medications can be distinguished between whether they mimic the same pharmacological action of the ''substance'' whose use should be stopped or reduced, or whether they target other more general pharmacological systems, that are supposed to be common to all SUDs, as they reflect the ''universal'' addiction process. The NbN offers obvious advantages, compared with previous classifications. In particular, it allows to no longer mix

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drugs with very different pharmacological targets under the same label. The main limitation of the NbN, when applied to psychopharmacology in general, and to SUDs medications in particular, is that drugs frequently have a ''dirty'' action, with multiple pharmacological targets. In this respect, it may be hard to classify drugs according to the NbN classification, without making the individual profile of each medicine more complex.

Abbreviations

ACNP	American College of Neuropsychopharmacology
AsCNP	Asian College of Neuropsychopharmacology
ATC	anatomical therapeutic chemical
AUD	alcohol use disorders
CINP	International College of Neuropsuchopharmacology
CNS	central nervous system
ECNP	European College of Neuropsychopharmacology
GABA	gamma-aminobutyric acid
HR	hazard ratio
IUHPR	International Union of Basic and Clinical Pharmacology
nAChRs	nicotine acetylcholine receptors
NbN	neuroscience-based nomenclature
NMDA	N-methyl-aspartate
NRTs	nicotine replacement therapies
OUD	opioid use disorders
SUDs	substance use disorders
TUD	tobacco use disorders
WHO	World Health Organization

Introduction

It is generally considered that the way of perceiving things results from how they are named. In the predominant usage of drug denomination, medicines are categorized according to the first or main therapeutic effect for which they have been used (e.g., ''antihypertensive drugs'', or ''antibiotics''). This also applies for drugs acting on the central nervous system (CNS), for example with labels such as ''antiparkinsonian drugs'', ''antidepressant drugs'', or ''anxiolytic drugs''. In this respect, the classification of the World Health Organization that is, the ''anatomical-therapeutic-chemical'' (ATC) nomenclature [1], is in line with this approach. The ATC provides five hierarchical levels of classification, as follows: 1) a first letter corresponds to the organ or systems of organs related to the action of the drug; 2) a doublet of figures that indicates the general symptomatic effect induced by the drug; 3) a letter that provides the main therapeutic action of the drug, that is, the main type of symptom, or set of symptoms, which the drug acts on; 4) another letter that indicates the biochemical class of drug; and 5) a last doublet of figures which corresponds to the name of the molecule. Table 1 provides an example of the ATC classification for diazepam.

However, psychotropic drugs are frequently used in different indications, which raises issues when the classification of the drug is based on its initial and/or primary indication [2]. A typical example of this is the instance of ''antidepressant drugs'', which have many more indications and efficacy areas than depression. Therefore, naming these drugs ''antidepressants'' impoverishes the understanding of their therapeutic potential, and can be a source of confusion, stigma, and non-adherence, among patients who receive these drugs for other indications than depression [1,3]. In this respect, International organizations, such as the European (ECNP), the American (ACNP), the Asian (AsCNP), and International (CINP) Colleges of Neuropsychopharmacology, as well as the International Union of Basic and Clinical Pharmacology (IUHPR), have pointed out these issues, and have commonly proposed an alternative nomenclature for classifying the drugs acting on the CNS. This new approach is the neuroscience-based nomenclature or ''NbN'' [4].

The NbN was initially proposed in 2014 [3], and then rapidly revised into a second and current version [1,4]. This revised version now includes 130 drugs. It is mainly based on the pharmacodynamic features of drugs, and reflects the updated knowledge on neurotransmission system and mechanisms of action. Furthermore, four additional dimensions have been added: 1) the official indications (as defined by international regulatory bodies); 2) updated evidence on both efficacy and safety; 3) practical aspects such as galenic formulations and conditions of use on the ground; and 4) evidence on neurobiological mechanisms of action (for illustration, see Table 2). As NbN is primarily based on pharmacology, new pharmacological targets and new molecules can easily been added into the nomenclature . This new approach is easy to handle and free of access on https://nbn2r.com/ [4].

The field of substance use disorders (SUDs) is not aloof of these conceptual issues. Actually, drugs approved for SUDs are labelled according to two main but different conceptual approaches. First, in line with what has been the usage in the neuropsychiatric field, medications for SUDs are classically defined according to their symptomatic effect. The main example of this is the frequent label of ''anticraving drugs'' [5,6]. This label describes the expected therapeutic effect, but not the idiosyncratic modes of action of the drug,

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Table 1 Principles of the 5-level WHO ''ATC'' nomenclature, using the example of diazepam.

	Denomination	Signification	Example of diazepam (N05BA01)
1	Letter	Anatomic group	N: nervous system
2	Doublet of figures	General class of drug, based on its symptomatic effects	N05: psycholeptic drugs
3	Letter	Main symptomatic effect	N05B: anxiolytics
4	Letter	Biochemical class of drugs	N05BA: benzodiazepines related drugs
5	Doublet of figures	Molecule	N05BA01: diazepam

ATC: anatomical-therapeutic-chemical; WHO: World Health Organization

Table 2 The six dimensions used in the NbN classification (based on Zohar et al., 2015) [1].

Dimension 1	Pharmacological domains	Acetylcholine, dopamine, GABA, glutamate, histamine, ion channel, lithium mimetic, melatonin, norepinephrine, opioid, serotonin
Dimension 2	Modes/mechanisms of action	Receptor agonist (full, partial), receptor antagonist, reuptake inhibitor (± and releaser or receptor antagonist); enzyme inhibitor, ion channel blocker, positive allosteric modulator (PAM), enzyme modulator
Dimension 3	Approved indication	Based on the recommendations of the major regulatory bodies (e.g. FDA, EMA, etc.)
Dimension 4	Efficacy and side effects	Evidence to support additional indication(s) as well as approved indication, for example expert guidelines + life-changing side-effects
Dimension 5	Practical notes	Clinical knowledge filtered through the taskforce « sieve »
Dimension 6	Neurobiology	Derived from empirical data and divided into preclinical and clinical sections, with an emphasis on the latter

EMA: European Medicines Agency; FDA: Food and Drug Administration; GABA: gamma aminobutyric acid; NbN: neuroscience-based nomenclature.

and thus frequently mixes molecules with radically distinct pharmacological mechanisms. Another approach is to define SUDs medication according to the main therapeutic strategy applied in a given type of SUDs. For example, the concepts of ''nicotine replacement therapies'' (NRTs), or ''opioid substitution medications'', suggests: 1) that these medications share a common pharmacological mode of action with that of the drug that has to be quitted, which is relatively in line with a NbN approach; and 2) suggest that these analog drugs should be used according to a specific treatment scheme, that is, prolonged ''replacement'' or ''substitution''. This is somewhat simplistic, as it implies that the drug of abuse and the medication do similar things, which is not exact, and it obscures the fact that these medications can be used in slightly different indications, for example for treating withdrawal symptoms.

This review proposes to display the approved medications used in SUDs according to the NbN classification, and to appraise the pros and cons of this new conceptual framework, compared to the classical way of labeling the drugs used in the field of SUDs.

List of drugs approved in SUDs according to the NbN

In line with the principle of the NbN, medications are displayed below according to their main pharmacological mode of action. Table 3 offers a synthesized comparison of medicine classifications, i.e., according to the former pre-NbN system on the one hand, and according to the NbN approach on the other hand.

Nicotinic drugs

Pharmacological principles

Nicotinic drugs mainly act as modulators of the nicotinic acetylcholine receptors (nAChRs). Acetylcholine is an important neurotransmitter in the brain, which is involved in many important physiological functions, such as mood regulation, vigilance, motility, memory, and learning [7–9]. Acetylcholine is also involved into reward processes, as it regulates the dopaminergic transmission in the mesolimbic

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Table 3 Pharmacotherapy of SUDs according to NbN approach, inspired from Nutt and Blier, 2016 [4].

Former terminology	NbN -Pharmacological based		Drugs
Indication based	Pharmacology	Mode of action	
Alcohol use disorder			
Alcohol withdrawal	GABA	Positive allosteric modulator, GABA-A receptor	Benzodiazepine (diazepam, oxazepam, etc.)
Maintenance of abstinence in alcohol dependence	Opioid	Antagonist (μ, δ, κ)	Naltrexone
	Glutamate GABA Calcium	Unclear	Acamprosate
	Aldehyde Dehydrogenase	Enzym inhibitor	Disulfiram
Reduction of alcohol consumption in adult patient with alcohol dependence	Opioid	Antagonist (μ, δ), partial agonist (κ)	Nalmefene
Reduction of alcohol craving in alcohol-dependent patient	GABA	GABA-B agonist	Baclofen
Opioid use disorder			
Opiate dependence (substitution therapy)	Opioid	μ partial Agonist κ antagonist Agonist	Buprenorphine Buprenorphine/naloxone Methadone
Adjunct to maintenance of abstinence in opioid dependence	Opioid	Antagonist (μ, δ, κ)	Naltrexone
Tobacco use disorder			
Smoking cessation	Acetylcholine	Nicotinic receptor agonist	Nicotine replacement therapies
Smoking cessation	Norepinephrine, dopamine	Reuptake inhibitor (NET, DAT), releaser (NE, DA)	Bupropion
Replacement (substitution treatment) and anti-craving substance for nicotine dependence and withdrawal	Acetylcholine	Nicotinic receptor partial agonist	Varenicline

DA: dopamine; DAT: dopamine transporter; GABA: gamma aminobutyric acid; NE: norepinephrine; NET: norepinephrine transporter; SUDs: substance use disorders; NbN: neuroscience-based nomenclature.

pathway, through the action of the nAChRs, in particular the α4β2 et α7 subtypes [10]. In practice however, nicotinic drugs are only approved and used for tobacco use disorder (TUD), in which nicotine is the main, if not the only, active principle that induces the addictive processes.

Available drugs

Nicotine replacement therapies (NRTs)

NRTs comprise a set of medications formulated to be absorbed through the oral (chewing gums, lozenges, sublingual tablets, inhaler/inhalators) or nasal mucosa (sprays), or through the skin (transdermal patches) [11]. Nicotine patches deliver a slow and passive nicotine dose throughout the day. Patches thus largely differ from tobacco use in terms of pharmacokinetics, which limits the occurrence of withdrawal. However, they do not replace the behavioral features of smoking.

The other types of NRTs mimic some of the hand-to-mouth characteristics of smoking, and their speed of action resembles more that of tobacco smoking, relative to nicotine patches. Transdermal patches are available in different daily doses, and deliver between 5 and 52.5 mg of nicotine over a 24 hour period resulting in plasma levels comparable to those observed between cigarette intakes in heavy smokers [12]. There are patches for 16 hours and others for 24 hours, the choice being based, among other things, on the presence of sleep disturbances or the presence of heavy cigarette cravings in the morning. Nicotine gums are available in both 2 mg and 4 mg formulations, and nicotine lozenges are available in 1 mg, 1.5 mg, 2 mg and 4 mg strengths, although the amount of nicotine absorbed by the user is less than the dose indicated [11].

NRTs are almost two-fold more efficacious (OR = 1.84, 95% CI = 1.71 to 1.99) for preventing relapse in tobacco use, compared to placebo [13]. The safety profile is generally favourable, as ADRs mainly consist of

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palpitations, headaches, insomnia, dizziness, dream disorders, and unspecific gastro-intestinal symptoms. In addition, these device can be used during pregnancy [14]. Overall, this makes NRTs a usual first-line option for supporting tobacco cessation in TUD.

While e-cigarettes and other vaping devices that deliver nicotine in water vapor can be assimilated as NRTs, and are both considered as similar harm reduction options by a majority of users [15], these products have not been considered as pharmaceutical products or pharmaceutical devices so far, and are thus not officially approved for supporting quitting.

Varenicline

Varenicline is a partial agonist of the $\alpha4\beta2$ nAChRs, with a high affinity for these receptors [16], which are particularly expressed within the reward system. In TUD, varenicline is supposed to have a double action. First, varenicline limits the binding of nicotine on this specific receptor subtype. Second, it constitutes a substitution of nicotine, and thus allows to reduce craving, but not all withdrawal symptoms, in subjects with TUD who have recently quit tobacco [17].

In a comprehensive meta-analysis, the efficacy of varenicline for supporting the cessation of tobacco use has been assessed as almost three-fold superior to that of a placebo (OR = 2.88; 95% CI = 2.40 to 3.47) [13]. However, though guidelines may vary from country to country, varenicline is frequently recommended as a second-line option, after failure of NRTs. This is for example the case in France [18].

Concerning its safety profile, varenicline-related ADRs include nausea, dream disorders, gastrointestinal symptoms, and more rarely mood alterations, with occasional suicidal ideations.

GABAergic drugs

Pharmacological principles

GABAergic drugs modulate the GABA system. GABA is the main inhibitory transmitter of the brain [19]. This action is crucial for maintaining the balance between the excitatory and inhibitory systems in the brain, and thus supports the regulation of many physiological functions of the CNS. Because the excitatory pathways are mainly supported by the glutamate/aspartate transmission, and because any modulation of the GABAergic (inhibitory) system also impacts the glutamatergic (excitatory) system, GABAergic drugs also indirectly modulate the glutamatergic system. Occasionally, they may also directly target both systems, by binding both GABAergic and glutamatergic receptors.

The GABA system involves two main classes of receptors: 1) ionotropic receptors, i.e., the GABA-A; and 2) metabotropic receptors, i.e., GABA-B receptors [19]. The ionotropic response is rapid and focused, while the metabotropic response is slower and more sustained in the brain. So far, all the available drugs approved for addictive disorders are agonists of the GABA receptors.

Available drugs

Benzodiazepines

Benzodiazepines are positive allosteric modulators of the GABA-A receptors. They are used only in alcohol use disorder (AUD) for preventing or treating alcohol withdrawal symptoms [20]. The main drugs used in this indication are diazepam and oxazepam. As benzodiazepines also have their own addictive potential, their use in this indication should be restrained to the detoxification period. Benzodiazepines have no demonstrated efficacy for preventing relapse into alcohol drinking, when used in the long run [21]. However, a preliminary comparative study has found that a prolonged (i.e., one-month-long) benzodiazepine treatment was associated with reduced craving and anxiety, and reduced relapse into heavy alcohol use, in a sample of recently detoxified subjects [22]. This suggests that other drugs acting on the GABA-A receptors, and with no addictive risk, could have an interest for reducing craving and relapse in AUD patients. Beyond the risk of addiction, the main ADRs of benzodiazepines comprise sedation, somnolence, ataxia, muscle relaxation, and memory deficits.

Baclofen

Baclofen is an agonist of the GABA-B receptors that are also a target in AUD [23]. Baclofen has been approved in France for supporting drinking reduction in AUD [24]. In this indication, the maximum daily dose is 80 mg per day. However, whether baclofen is efficacious and what should be the maximum dose approved in AUD remain under debate [25,26].

A couple of studies have also suggested that baclofen could be efficacious for preventing withdrawal symptoms in AUD [25]. However, baclofen has also been associated with an increased risk of seizures [27,28], and the risk benefit ratio of using baclofen in this indication is poor, relative to benzodiazepines, which have a well-demonstrated anti-epileptic effect [25]. At this stage, baclofen should thus not be used in this specific indication. In terms of safety, the most frequent type of ADRs are related to sedation, i.e., somnolence, dizziness, and associated accidents and falls [25]. More serious ADRs can occur, including confusion, seizures, coma, hallucinations, and specific withdrawal syndrome [27].

Opioid drugs

Pharmacological principles

Opioid drugs modulate the opioid receptors, which are involved in important brain functions, such as the regulation of pain, reward, and mood [29]. Three main types of opioid receptors are met in the central nervous system, i.e., the μ, δ, and κ receptors. Endogenous opioid ligands are the beta-endorphin, enkephalins, dynorphins, or the neoendorphin. This neurotransmission system is of course deeply involved in the triggering of opioid use disorder (OUD). Furthermore, opioid molecules are supposed to regulate the transmission of dopamine in the ventral striatum, through the complex action of the μ and δ receptors of the nucleus accumbens [30]. δ-receptor agonists are supposed to induce a reinforcing effect on reward processes, though this effect seems to be less important than that of μ-receptor agonists. Regarding the dynorphin/κ receptor system, it seems to downregulate the dopamine transmission in the mesolimbic system [31].

For all these reasons, opioid drugs have a double function in the therapeutic arsenal of addictive disorder. Some drugs, in particular opioid agonists, are specifically involved

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in OUD. In contrast, other drugs, in particular μ antagonists, have a more general use in addictive disorders, even if they have been specifically approved for AUD until now.

Available drugs

Naltrexone

Naltrexone is an antagonist of the μ, δ, and κ receptors. Naltrexone is approved in several countries for OUD, essentially under the formulation of extended-release injectable formulation [32]. Naltrexone is supposed to foster the desensitization from opioids, because of its antagonist effect, thus reducing craving and relapse risks. To avoid precipitating a severe withdrawal, it is typically administered after a short period of abstinence [33].

A study conducted on criminal justice offenders found a lower risk of relapse among extended release of naltrexone patients compared to treatment as usual (hazard ratio [HR] = 0.43; 95%CI = 0.28 to 0.65, $P < 0.001$) but the effect did not persist approximately one year after the end of the treatment phase [34].

Extended-release naltrexone is ideally recommended in detoxified OUD patients who exhibit current criteria for AUD, or in ''persons with a short or less severe addiction history or who must demonstrate to professional licensing boards or criminal justice officials that their risk of opioid use is low'' [35].

Naltrexone is also approved in AUD, for the maintenance of abstinence from alcohol. In this indication, naltrexone is mainly used on oral formulations, though approval with the extended release injection form also exist in some countries [36]. In AUD, naltrexone is a first-line option, together with acamprosate. However, naltrexone is less efficacious than acamprosate for supporting abstinence. In contrast, naltrexone is more efficacious than acamprosate for limiting the severity of relapse, in case of relapse [37]. The overall safety of naltrexone is acceptable, though less good than that of acamprosate. More specifically, naltrexone exposes to non-specific gastrointestinal symptoms, insomnia, anxiety, nervousness, cramps, fatigue, joint or muscle pain, headaches.

Nalmefene

Nalmefene is also an antagonist of the μ and δ receptors, but, in contrast with naltrexone, it is a partial agonist of the κ receptors [38]. This latter mechanism of action would confer nalmefene a greater efficacy on craving in AUD. Nalmefene is usually approved in first-line for supporting drinking reduction in AUD [20]. However, the exact level of efficacy of nalmefene has been questioned by meta-analyses [39]. The main ADRs associated with nalmefene are nausea, dizziness, insomnia, and decreased appetite.

Methadone

Methadone is full-agonist of the μ receptors, and a N-methyl-aspartate (NMDA) receptor antagonist, with a half-life of 24 to 36 hours. Methadone has been the first approved opioid maintenance treatment [40]. However, despite the fact that its use improved health and social condition of patients, and that it is still the most frequently prescribed treatment for OUD, its prescribing raises several safety concerns. Indeed, due to its full agonist properties, methadone exposes to a higher risk of overdose, in particular during the initiation phase of the treatment, and/or in case of insufficient supervision [40]. In order to reduce the risk of overdose, methadone delivery is subject to greater constraints. Measures to minimize diversion include ensuring good access to treatment and administering doses under direct observation [41,42]. For example, in the United States and in France, methadone is only available via clinic-based programs and is administered mainly under direct observation, whereas buprenorphine can be prescribed by trained doctors, while medication intake does not need to be directly observed [41].

Buprenorphine

Buprenorphine is a partial agonist of the μ receptors, and an antagonist of the κ receptors. Buprenorphine has a long half-life ranging from 24 to 48 h. The affinity of buprenorphine for μ receptors is very elevated [43]. This double feature, i.e., partial agonist plus high affinity, makes buprenorphine association with full-agonist harmful, because of an important risk of withdrawal [44]. However, the nature of partial agonist of buprenorphine makes this drug of much lesser risk of overdose, relative to methadone.

By contrast, buprenorphine can be easily diverted and misused through intravenous or intranasal use [42]. It is considered that approximately 20% of buprenorphine prescriptions are diverted [40]. In this respect, forms associated with naloxone have been developed to reduce the risk of misuse, though these galenics do not allow a complete suppression of misuse and diversion [45]. New formulations of long acting buprenorphine depots or implants are being approved and commercialized throughout the world [46]. Though these new formulations may theoretically reduce misuse, they will more likely interest subjects with OUD who do not divert buprenorphine, but are attracted by comfort and recovery aspects [40].

Slow-release morphine

Oral slow-release morphine is approved as opioid maintenance treatment in some countries. Morphine acts as a pure agonist on opioid receptors and slow-release preparations of morphine results in sustained blood concentration for 24 h after once-daily oral administration. It has been found that this treatment was as effective as methadone in the treatment of OUD with comparable safety and tolerability [47,48], and a greater benefit on patient wellbeing [47].

Regarding opioid-related safety issues, the main type of ADRs are related to opioid overdose, though this medical consequence more rarely occurs using buprenorphine. Agonist opioid medications can also trigger constipation, nausea and vomiting, confusion, dysuria and urinary retention, pruritis, and addiction. Methadone can specifically prolong the QT interval.

Other classes of drugs

Pharmacological principles

Other neurotransmission systems, such as glutamate, dopamine or noradrenalin, are targeted by drugs approved in SUDs. Moreover, mechanisms of action involving other principles than neurotransmission, e.g., enzyme regulation, also belong to the therapeutic arsenal of SUDs.

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Available drugs

Acamprosate

Acamprosate has been historically considered as a GABAergic drug, as it has a similar chemical structure to that of the GABA, and has been hypothesized to modulate the action of the GABA-A receptor [49]. However, recent evidence has questioned the direct effect of acamprosate on the GABA system, and has suggested that acamprosate could more likely modulate the N-methyl-d-aspartic acid receptor transmission [50]. Other modes of action have also been suggested, including the activation of sodium channels or the modulation of the synaptic levels of glutamate and beta-endorphin. This highlights the limitations of the NbN approach, for classifying drugs with pleiotropic actions in the brain.

Acamprosate is indicated in AUD, with the indication of a support for maintaining abstinence after a detox process. In this indication, it would reduce the risk of relapse in alcohol use [37]. In contrast, it has shown no efficacy for supporting drinking reduction. It is well tolerated, the main ADRs being nausea and diarrhoea, and constitutes one of the two first-line medications for supporting abstinence maintenance in AUD [20].

Bupropion

Bupropion is an inhibitor of the catecholamine (dopamine and noradrenaline) transporter, which also possesses an antagonist action on the nicotinic receptors of the CNS [2]. Bupropion is approved for supporting the cessation of tobacco use, in add-on with NRTs. It provides limited additional efficacy, compared to NRTs alone. Indeed, there is high-level evidence that bupropion increases long-term smoking cessation rates (RR = 1.64, 95%CI: 1.52 to 1.77). However, there is also insufficient evidence to establish whether add-on bupropion and NRTs result in superior quit rates, relative to NRTs alone (RR = 1.19, 95% CI 0.94 to 1.51), or whether add-on bupropion and varenicline result in superior quit rates, relative to varenicline alone (RR = 1.21, 95% CI 0.95 to 1.55). Concerning safety data, despite insufficient evidence to establish whether patients taking bupropion are more likely to report serious adverse events compared to patients taking placebo (RR = 1.16, 95% CI 0.90 to 1.48), there is high-level evidence that use of bupropion results in more trial dropouts due to adverse events of the drug than placebo (RR = 1.37, 95% CI = 1.21 to 1.56) and that patients taking bupropion experienced more psychiatric adverse events in comparison to placebo (RR = 1.25, 95% CI 1.15 to 1.37) [51]. Others ADRs comprise agitation, dry mouth, constipation, and seizure risk.

Disulfiram

Disulfiram is approved for AUD, as a second line option for supporting abstinence maintenance [20]. However, in this indication, disulfiram has no direct action in the CNS. Disulfiram acts by blocking aldehyde dehydrogenase in the liver, thus inducing an increase of acetaldehyde concentration in the blood in case of alcohol use. This mode of action is related to the so-called ''antabuse'' effect of disulfiram, which consists of the occurrence of flush, tachycardia, increased blood pressure, and nausea, in the case of alcohol abuse with disulfiram [52,53]. The main ADRs of disulfiram are headaches, fatigue, sleepiness, anxiety, hepatotoxicity and peripheral neuropathy.

Discussion

The objective of this review was to display the different categories of medications approved in the field of SUDs, according to the NbN, and to appraise the pros and cons of using the NbN, compared with symptom-based classifications of drugs.

Compared with psychiatric and neurological disorders, and even with behavioral addictions, SUDs exhibit a very original feature, which is that SUDs are related to the use of a pharmacological compound, or a set of pharmacological compounds, i.e., the ''substance''. When this ''substance'' corresponds to one unique molecule, for example heroin or cocaine, this molecule possesses its own pharmacological action in the brain. In that sense, it could also be defined according to the NbN, even if it is not used as a pharmacotherapeutic agent. This was not possible in the symptom-based nomenclatures. In some cases, a ''substance'' corresponds to a natural product, consisting of a vast array of psychopharmacological agents, which may have different or even opposite pharmacological effects. For example, it has been found that the two main compounds of cannabis, i.e., Δ-9 tetrahydrocannabinol on the one hand, and cannabidiol one the other hand, have opposite effects on the cannabis receptor CB-1 [54]. Natural products may thus have a more complex and subtle action on the CNS.

Based on this preliminary consideration, applying a NbN approach to the medicines used in SUDs allows to differentiate from two main neurobiological types of drugs: 1) those which share the main pharmacological features than those of the drug which is aimed to be quitted; and 2) those which modulate other pharmacological targets than those of the drug which should be quitted. In the latter case, these targets may be common between the different SUDs, and be related to the theory of a general addiction process which share common features, whatever be the underlying substance of the SUD. This theory generally pertains to dopamine transmission in the ventral striatum, through the mesocorticolimbic axis [55]. In this instance, opioid antagonists such as naltrexone, or, to a lesser extent, nalmefene, are supposed to block the dopaminergic mesolimbic axis, and thus to have an ''pan-addiction'' action, including with respect to behavioral addiction such as gambling disorder or video gaming disorder [56]. This should be nuanced however, as the role of dopamine in several types of SUDs has been questioned, for example in OUD or cannabis use disorder [57].

By contrast, drugs that act on the similar pharmacological targets than the ''substance'' that is supposed to be stopped are used in first line for suppressing withdrawal symptoms. This is the case of benzodiazepines in AUD, of methadone and buprenorphine for OUD, or of NRTs for TUD. While these drugs are not approved yet, this is also the case for tetrahydrocannabinol plus cannabidiol in cannabis use disorder [58]. In some instances, but not all, pharmacological analogs to the ''substance'' may be use on the long run, with the aim to support abstinence or reduce substance use. This is typically the case for opioid agonist treatments

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or NRTs. This ''substitution'' approach has also been suggested for baclofen in AUD, as both ethanol and baclofen target the GABA-B receptors [21]. It has been questioned regarding the chronic use of benzodiazepines in AUD, essentially because of safety reasons [21], and despite the fact that some preliminary data may support the benefits of prolonging benzodiazepine use at least one month after alcohol withdrawal in AUD [22].

The main advantage of using the NbN for naming medications used in SUDs is that it allows not mixing under the same label (for example ''anticraving drugs'') medications that have completely different pharmacological effects (for example opioid antagonist on the one hand, and GABA allosteric modulation or NMDA antagonism on the other hand). Designating drugs by the pharmacological mode of action, and then by the indication, as the NbN does, offers more clarity and consistence. However, the main disadvantage for using this system is that the pharmacological effects of medications are rarely unique. On the contrary, pharmacological effects are frequently ''dirty'', with multiple actions and multiple targets. In this respect, it may be much more difficult to classify medications, as their action may result from a mix of several pharmacological effects. The best example of this is acamprosate, whose mode of action is certainly complex and multiple. It is thus hard to state whether acamprosate is GABAergic drug, as it was initially supposed to be, or more a glutamatergic drug, or even something else.

This constitutes the main limitation of applying the NbN to psychotropic drugs in general, and to SUDs' medication in particular. This is also an important limitation of this review. Another limitation is that we have only focused on approved drugs, whereas several pharmacological drugs, involving other pharmacological systems, are promising options for SUDs and even for behavioral addictions. For example, the glutamatergic drug topiramate has shown very promising prospects in AUD and cocaine use disorder [59,60], as well as in binge eating disorder [61]. Another example is the increasing prospects of cannabidiol in several SUDs, including AUD [54]. Even if we chose to use a conservative approach in this review, the NbN should not be restricted to approved drugs in general. Another issue is that the paradigm shift proposed by the NbN approach requires a thorough knowledge regarding the pharmacokinetic and pharmacodynamic features of psychotropic drugs. This has to be associated with appropriate evidence-based education during, and after, medical studies. Finally, even if the NbN classification, initially including 107 medications, was already expanded over a few years to 130 listed medications in the second edition, it is still evolving. Some drugs cited in this review (NRTs, slow-release morphine) are not, to our knowledge, listed in the official application.

In conclusion, applying the NbN for classifying the medications of SUDs provide a more consistent and systematic approach, relative to the former denominations that could mix very different drugs under the same label. This change of paradigm has already begun with the concept of opioid agonist treatment, which slowly replaces that of opioid substitution treatment. The main issue of this new conceptual framework however, is that psychopharmacological compounds are rarely pure in their targets and actions, and that it can be difficult to classify molecules according to their pharmacological effect, when these effects are actually widespread and very heterogeneous.

Disclosure of interest

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