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Eric Konofal, Michel Lecendreux, Jean-Charles Bizot, Anh-Tuan Lormier, Bruno Figadère. NLS-3 (Levophaceterane or (R,R) Phaceterane): A Reverse Ester of Methylphenidate: A Literature Review. *Current Medicinal Chemistry*, 2024, 31 (9), pp.1069-1081. 10.2174/0929867330666230120161837 . hal-04284826

HAL Id: hal-04284826

<https://hal.science/hal-04284826v1>

Submitted on 14 Nov 2023

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NLS-3 (levophaceterane or (*R,R*) phaceterane), the reverse ester of methylphenidate: a literature review.

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Abstract

Background: NLS-3 or (R,R) enantiomer of phacetoperane (levophacetoperane) is the reverse ester of methylphenidate, a well-documented psychostimulant marketed for the treatment of attention-deficit/hyperactivity disorder (ADHD) since the end of 1950s. Launched on the market in Canada and in Europe, by Specia - Rhône-Poulenc, and Rhodia, market named Lidepran® (8228 R.P.), targeting obesity and depression, has benefited from 1959 to 1967 of an increasingly popularity in psychiatry. Previous data supported that the stimulant effect of phacetoperane differed from those of other medications acting on the catecholamines system (e.g. methylphenidate, amphetamine), with an advantage on benefit/risk balance. Method: The goal of this study is to better characterize the binding profile of NLS-3 using *in vitro* and *in vivo* assays and to hypothesize potential indications considering the literature. Results: A complete binding profile assay confirmed the potential benefit of phacetoperane with a higher benefit/risk compared to other stimulants. NLS-3 synthesis resulted from phenylketone also used for the synthesis of methylphenidate. It differs from that used by Rhône-Poulenc SA laboratories, allowing the possibility of individualizing several enantiomers never synthesized beforehand. The present international review also confirmed an extended clinical experimentation of the compound including almost one thousand children and adolescents in large doses-range with less side-effects than with comparative treatments. Furthermore, levophacetoperane was generally well-tolerated by the subjects. Conclusion: The NLS-3 could be more a safe and more potent alternative to stimulants on the market for patients with ADHD.

Introduction

More than 80 years ago [1], scientific literature increasingly pointed out that psychostimulants could significantly reduce the symptoms of such disorders as attention-deficit/hyperactivity disorder (ADHD) or narcolepsy. Today, only two active stimulant medications are approved on the international drug market, methylphenidate and amphetamine salts.

Pharmacological treatments are essential for the management of such neuropsychiatric disorders among children, adolescents and adults, and stimulant-based medications (methylphenidate and amphetamines) are the most effective compounds. Psychostimulants are used first line and nonstimulants second-line, unless there is a strong contraindication [2]. The approval by the authorities of psychotropic drugs with novel mechanisms of action has been extremely rare in recent years and above all failed to rise better efficacy than stimulants excepted for mazindol, an imidazo-isoindole compound, originally developed as an appetite suppressant, known as a tricyclic agent unrelated to amphetamine, enhancing wakefulness and arousal, previously used in narcolepsy with cataplexy and acting on ADHD symptomatology [3,4].

However since 40 years, no new psychostimulant targeting arousal-related disorders has entered the market, when ADHD is the most common neurobehavioral disorder with an estimated worldwide prevalence of at least 5% in children and 3-5% in adults [5,6], and when narcolepsy with cataplexy reduces daily functioning and is associated with a substantial medical and economic burden, with many patients being on full disability with an annual direct medical costs estimated approximately 2-fold higher in them than in general population [7].

Despite of an impressive history that began in 1944, methylphenidate, which is still widely studied in both clinical and research settings, experienced only its large development at the end of the 1960's [8].

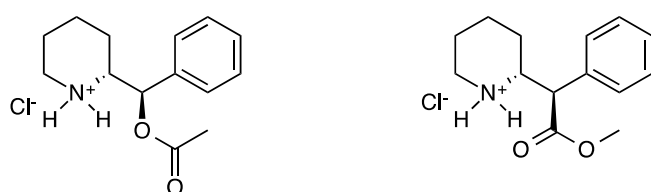
Previously indicated in 1955 for chronic fatigue syndrome, asthenia, lethargic and depressed states, including those associated with tranquilizing agents and other drugs in adult [9], methylphenidate has become, since 1963, the only drug used to treat hyperkinetic disorder and related behaviors [10,11].

Methyl 2-phenyl-2-(2'-piperidyl)-acetate or ($\alpha R, 2R$)- α -phenyl-2-piperidinemethanol acetate, its reverse ester, is another substituted phenethylamine synthesized at the end of the 1950's and primarily developed by Bayer (phenylpiperidylcarbinol, Bayer 1313) and Rhône-Poulenc as racemic salt (7890 R.P.), and later as levophacetoperane (8228 R.P., SKF-9946) and brand-named Lidepran® in 1961 (Société Parisienne d'Expansion Chimique, Specia, Rhône-Poulenc laboratories). It was prescribed for the treatment of oligophrenia and

psychasthenia and benefited from a wealth of clinical trials and experiments that methylphenidate never obtained during this period of time.

Levophacetoperane or (R,R) phacetoperane was not considered as a direct psychostimulant but as a psychoanaleptic agent, because it was almost devoid of sympathomimetic effects [12]. Whilst its exact mechanism of action is unclear phacetoperane (Figure 1, chemically and pharmacologically close to methylphenidate, (R,R) has been shown to bind -the catecholamines transporter to potently inhibit dopamine and norepinephrine uptake,.

(R,R) phacetoperane and the (S,S) enantiomer, both have been considered as new chemical entities and granted for the treatment of ADHD under the registration number (R71 (3) EPC), published first in 2011 (EP2785344 B1) by the European, and after by Japanese, U.S. and Canadian Patent Office [13].



(R,R) phacetoperane (1)

(R,R) methylphenidate (2)

Figure 1. Structures of phacetoperane and methylphenidate

Many non-stimulant and stimulant agents such as amphetamine salts and a large number of various methylphenidate release systems have been licensed, but the occurrence of adverse events including cardiovascular effects, encourages scientific community to promote pharmacological alternatives.

Today, the gold-standard treatment for ADHD and narcolepsy remains methylphenidate, with no known alternative. (R,R) phacetoperane (NLS-3) is effective to treat global arousal-related disorders without presenting hemodynamic adverse effects. A careful analysis of the literature together with an analysis of recent findings is strongly in favor of NLS-3.

Synthesis and chemical properties of (R,R) phacetoperane

Structurally, (R,R) phacetoperane (NLS-3), as a reverse ester of (R,R) methylphenidate (2), could be obtained from the same key phenylketone (3) as methylphenidate, (Figure 2) [14]. (R,R) phacetoperane was thus derived from compound (3) after reduction, acetylation and protecting group removal (Figure 2). (R) -N-Boc-pipecolic acid (5) is commercially available; it was efficiently converted to the N,O-dimethyl hydroxamate by treatment with N,O-dimethylhydroxylamine hydrochloride in the presence of triethylamine (TEA) and benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) in dichloromethane (CH₂Cl₂) at room temperature for 6 h. Weinreb amide (4), so obtained, was

then treated with phenyllithium in Et₂O at -23°C to furnish the key phenylketone (3) in 68 % yield, and without epimerisation [15].

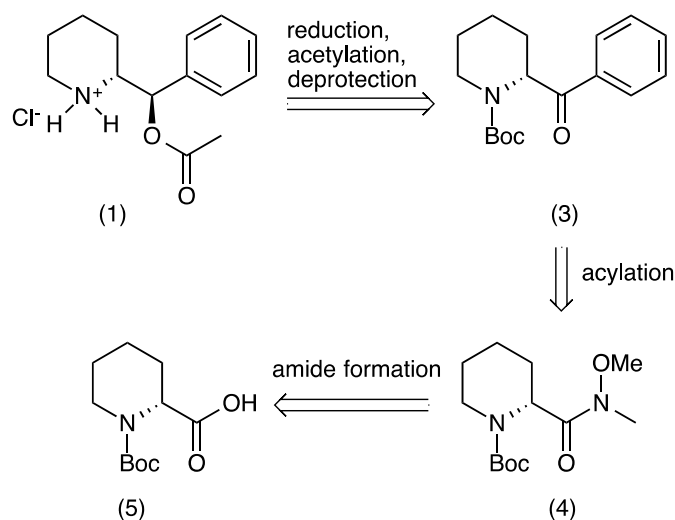


Figure 2. Retrosynthetic approach to (*R,R*) phacetoperane (NLS-3)

Phenylketone (3) was then reduced by treatment with one equivalent of L-Selectride® at -78°C in THF, to obtain the expected *syn* alcohol in a Felkin-Ahn fashion selectivity (*dr* > 95:5) and in 65 % isolated yield.[16] Then, alcohol (6) was acetylated by treatment with acetic anhydride to afford the expected acetate (7)[17] which was then treated by hydrochloric acid to give the desired (*R,R*) phacetoperane as the hydrochloride salt (1) in 68 % yield (Figure 3) [18].

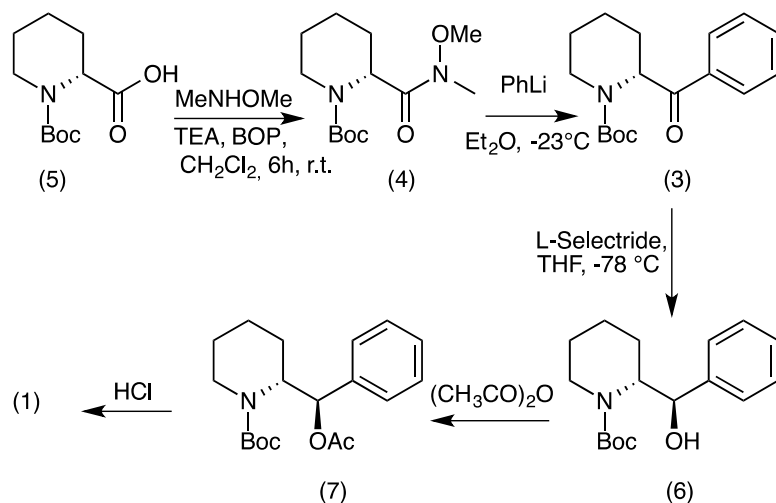


Figure 3. Synthesis of (*R,R*) phacetoperane (NLS-3)

In summary, the total synthesis of (*R,R*) phacetoperane (1) was newly performed in 5 steps, in 20 % yield and with >99 % ee, starting from commercially available (*R*)-pipecolic acid. Interestingly, starting from (*S*)-pipecolic acid, (*S,S*) phacetoperane could be obtained in 99% ee as well and in 25 % overall yield.

This chemical preparation used, which stands out and differs from that used by Rhône-Poulenc SA laboratories for the new esters of 2-piperidylphenyl-methanols and ethanols derivatives synthesis [19–21] therein could be applied to the synthesis of phacetoperane derivatives bearing, for instance, functional groups on the phenyl ring, opening the path to structure-activity relationship studies [13].

***In vitro* psychopharmacology profile**

It has been primarily reported that levophacetoperane (or (R,R) phacetoperane) as well as amphetamine, inhibited *in vitro*, in a competitive manner, norepinephrine uptake, in rat hypothalamus and cortex and dopamine uptake as well in corpus striatum and cortex, when at higher concentration, alone amphetamine inhibited serotonin (5-HT) uptake in hypothalamic ganglia [22]. In this previous study, in accordance to Snyder and Cole experimental procedures [23], amphetamine and levophacetoperane had been shown to be powerful NA and DA re-uptake inhibitors in hypothalamic ganglia and corpus striatum at a concentration of 10 μM , with an inhibition up to 50% (Table 1).

| Compound | Inhibition of [^3H]monoamine uptake ($K_i = \mu\text{M}$) [‡] | | | |
|---------------------------------|---|-------------------------|---------------------------------|------------------------|
| | [^3H]-Dopamine | | [^3H]-Norepinephrine | |
| | Hypothalamus | Cortex | Corpus striatum | Cortex |
| Concentration (μM) | 0.1 | 0.1 | 0.5 | 0.1 |
| Amphetamine | 0.27 ^{‡,***} | 0.11 ^{‡,****} | 1.19 ^{‡,*} | 0.13 ^{‡,****} |
| Concentration (μM) | 0.1 | 0.25 | 1 | 0.25 |
| Levophacetoperane | 0.115 ^{‡,****} | 0.127 ^{‡,****} | 0.86 ^{‡,***} | 0.22 ^{‡,****} |

Table 1. Inhibition of [^3H]-monoamine uptake into rat brain synaptosomes by amphetamine and levophacetoperane *in vitro*

This primary study on cerebral tissue homogenates of Sprague Dawley male rats, and based on inhibition of ^3H -dopamine and of ^3H -norepinephrine, showed a high affinity for DA ($K_i = 0.115$ and $0.127 \mu\text{M}$) and for NA ($K_i = 0.86$ and $0.22 \mu\text{M}$) for levophacetoperane and expressed an excellent central nervous system penetration profile (Table 2).

| Compound | (R,R) phacetoperane | (S,S) phacetoperane |
|---|---------------------|---------------------|
| Dopamine transporter (h) ^a | 98.6% | 82.3% |
| Norepinephrine transporter (h) ^a | 89.8% | ** |
| k (KOP) ^b | ** | 31.4% |
| M ₁ (h) ^a | ** | 29.6% |
| M ₃ (h) ^a | 31.3% | 44.7% |
| Y ₁ (h) ^b | 27.1% | ** |

^aantagonist radioligand

^bagonist radioligand

** <25% Inhibition of Control Specific Binding

Table 2. Compounds (*R,R*) phacetoperane and (*S,S*) phacetoperane binding activity

| Compound | (<i>R,R</i>) phacetoperane | (<i>S,S</i>) phacetoperane |
|--|------------------------------|------------------------------|
| Dopamine transporter (<i>h</i>) ^a | 98.6% | 82.3% |
| Norepinephrine transporter (<i>h</i>) ^a | 89.8% | ** |
| k (KOP) ^b | ** | 31.4% |
| M ₁ (<i>h</i>) ^a | ** | 29.6% |
| M ₃ (<i>h</i>) ^a | 31.3% | 44.7% |
| Y ₁ (<i>h</i>) ^b | 27.1% | ** |

^aantagonist radioligand
^bagonist radioligand
** <25% Inhibition of Control Specific Binding

Futhermore, results from this re-uptake study indicated that levophacetoperane has no effect on 5-HT levels, when it could be detected on striatum and cortex with amphetamine. From previous findings, it has been speculated that levophacetoperane could be less addictive in animal models than amphetamine [22,24].

Following these previous findings, a standard panel of molecular targets of (*R,R*) phacetoperane and (*S,S*) phacetoperane tested at 10 µM has been launched by NLS Pharmaceuticals (*unpublished data*; Study # 100024052, Eurofins Cerep, 2015, France) (Table 2).

| Compound | (<i>R,R</i>) phacetoperane | (<i>S,S</i>) phacetoperane |
|--|------------------------------|------------------------------|
| Dopamine transporter (<i>h</i>) ^a | 98.6% | 82.3% |
| Norepinephrine transporter (<i>h</i>) ^a | 89.8% | ** |
| k (KOP) ^b | ** | 31.4% |
| M ₁ (<i>h</i>) ^a | ** | 29.6% |
| M ₃ (<i>h</i>) ^a | 31.3% | 44.7% |
| Y ₁ (<i>h</i>) ^b | 27.1% | ** |

^aantagonist radioligand
^bagonist radioligand
** <25% Inhibition of Control Specific Binding

Compounds binding was calculated as a % inhibition of the binding of a radioactive labeled ligand specific for each target. This binding assay panel was broadly defined with roughly an equal number of selective, central and peripheral therapeutically relevant targets, including native animal tissues, radioligands and specific enzymes involved in cell cycle regulation.

For radioligand binding experiments, the half maximal inhibitory concentration (IC_{50}) and the half maximal effective concentration (EC_{50}) values were determined (*via* computer software) by nonlinear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants (K_i) were calculated using Cheng–Prusoff equation ($K_i = IC_{50}/(1+(L/K_D))$), where L is the concentration of radioligand in the assay, and K_D is the affinity of the radioligand for the receptor [25]. The results are expressed as a % control specific binding ($[(\text{measured specific binding}/\text{control specific binding}) \times 100]$) and as a % inhibition of control specific binding ($100 - [(\text{measured specific binding}/\text{control specific binding}) \times 100]$) obtained in the presence of the test compounds. An inhibition or stimulation of more than 50% is considered as a significant effect of the test compounds and between 25% and 50% indicated of weak to moderate effects that should be confirmed by further testing as they are within a range where more inter-experimental variability can occur. Fifty percent is a common cut-off for further investigation (i.e. determination of IC_{50} or EC_{50} values from concentration-response curves).

Table 2 displays the effects for (*R,R*) phacetoperane and (*S,S*) phacetoperane.

The primary pharmacological targets for (*R,R*) phacetoperane, or NLS-3, are the dopamine transporter (DAT) and the norepinephrine transporter (NET). In results to these binding assays, (*R,R*) phacetoperane or NLS-3 exhibited appreciable potencies for DAT (98.6% inhibition of control specific binding) and NET (89.8% inhibition of control specific binding) when the (*S,S*) phacetoperane only blocked DAT (82.3% inhibition of control specific binding) (*unpublished data* ; Study # 100024052, Eurofins Cerep, 2015, France). Blockade of these neurotransmitter transporters results in decreased presynaptic re-uptake following release and increased average neurotransmitter concentrations in the synaptic cleft.

Additional competition binding experiments for NLS-3 and (*S,S*) phacetoperane have shown no activity at 10 μM for the human serotonin transporter (SERT), any of the serotonin, histamine, adrenergic receptors. However, a weak antagonist binding to several muscarinic subtypes has been observed for (*S,S*) phacetoperane on M_1 receptors (29.6% inhibition of control specific binding) and M_3 receptors (44.7% inhibition of control specific binding) and for NLS-3, but only on M_3 receptors (31.3% inhibition of control specific binding). These binding activities may contribute to the remarkable efficacy of these compounds – these targets are shared by drugs in development for treating neurodegenerative diseases such as Parkinson’s disease and were pointed out for their interest for asthma and airway obstructions since a long time.[26]

With a lowest binding activity, (*S,S*) phacetoperane also showed little affinity to Kappa Opioid Receptors (KOP-r), thus can be clinically considered but being very weak (31.4% inhibition of

control specific binding) (*unpublished data*; Study # 100024052, Eurofins Cerep, 2015, France).

KOP-r partial agonists can be hypothesized as a pharmacotherapeutic strategy for cocaine addiction and relapse[27–31]. It has been proposed that KOP-r agonists oppose the effects of drugs, such as cocaine, by modulating the dopamine system.[32,33] Thus KOP-r ligands (including partial agonists) are relevant for the treatment of addiction and behavioral sensitization[34–37].

Animal experiments

Primary preclinical investigations, based on animal, showed a low risk of toxic effect of levophacetoperane (levofacetoperane or 8228 R.P.) in rodents and dogs for different routes of administration (*per os*, subcutaneous, intravenous).

Acute toxicity estimations were based on 10-animals/dose levels and a one-week observation time. The single doses that kill half of the experimental animals (LD50) values in mice were 390 mg/kg (PO), 300 mg/kg (SC) and 77 mg/kg (IV). In rat, LD50 were 400 mg/kg (PO), 400 mg/kg (SC) and 80 mg/kg (IV). Rodents poisoning was signaled by a coordinated hyperactivity, without phase of consecutive depression, for the sublethal doses. At clearly toxic doses, there appear tremors, disordered convulsions; death occurs by respiratory arrest.[19,20,24,38,39]

Daily administration of 5 mg/kg of levophacetoperane by mouth to dogs caused psychomotor excitation only after 15 days of treatment. Intoxication at sub-lethal doses was marked by coordinated hyperactivity without a subsequent stage of depression. Toxic doses produce tremor and incoordinate convulsion. Levophacetoperane had little or no effect on blood pressure, cardiac rhythm, or on respiratory rate and amplitude, but produces stimulation of locomotion in dogs, without subsequent depression, at a dose level of 5mg/kg.[40]

In whole studies, levophacetoperane was comparable to methylphenidate in terms of central stimulation activity but with lower sympathicomimetic effects[19,38,41], and acute toxicity of levophacetoperane by oral (PO), subcutaneous (SC) or intravenous (IV) routes administration was much lower than methylphenidate and amphetamine.[38]

Repeated and prolonged administrations, for one month, of high oral doses of (R,R) phacetoperane were only performed in rats and dogs.

Chronic intoxication using sublethal doses of drugs was behavioral expressed in these different animal species by a coordinated motor hyperactivity without consecutive depression phase. At highest toxic doses, tremors appeared, disordered convulsions, and finally death, which occurred by respiratory arrest.

The animals treated with levophacetoperane, in comparison with methylphenidate and especially with amphetamine, were not irritable, so that they could be handled without becoming aggressive[38].

Handling animals during experimentation can worsen their mortality when subjected to sublethal doses. The influence of calm and isolation on toxicity has also been studied. Unlike methylphenidate or amphetamine, levophacetoperane did not increase the mortality rate of animals handled by causing nervous exhaustion in them[24,38].

The results showed also that if, in general, the LD50 was lower in isolated animals than in grouped animals, the difference was quite small with regard to levophacetoperane (Table 3).

| Compound | Route | LD50 (mg/kg) in mice | |
|-------------------|-------|----------------------|----------|
| | | grouped | isolated |
| Levophacetoperane | SC | 305 | 330 |
| | PO | 325 | 370 |
| Methylphenidate | SC | 190 | 350 |
| | PO | 180 | 210 |
| Amphetamine | SC | 15 | 125 |
| | PO | 97 | 100 |

Table 3. Comparison of LD50 between levophacetoperane, amphetamine and methylphenidate

Results for these two modes of housing showed that irritability by reciprocity was negligible with levophacetoperane, unlike with methylphenidate and especially amphetamine; this was arguing in favor of the weak sympathomimetic action of levophacetoperane.[24,38,40]

The chronic toxicity experimented at LD50 doses of levophacetoperane, as well as that of all central stimulants, depended on multiple factors such as age and weight of the animals. Also, young animals appeared to be more resistant[38,42].

Compared to methylphenidate, with which it shares >90% of its pharmacological similarities, levophacetoperane was lesser toxic at equivalent doses, in all the studies carried out, whatever the animal's species[41].

Levophacetoperane or NLS-3 (3 mg/kg) has expressed less addictive effects in 7-8 weeks old male C57BL/6J mouse than d-amphetamine (2 mg/kg) and methylphenidate (6 mg/kg) in open-field.

Results of these animal experiments inducing a pharmacological and contextual sensitization, and a cross-sensitization to d-amphetamine have been partially presented at the 4th Eunethydis International Conference[43] and described in the U.S. Patent Application No. 15/913,481, entitled: Phacetoperane for treating of attention deficit hyperactivity disorder[13].

Past clinical reports and studies

Since the 1960's Levophacetoperane or (R,R) phacetoperane is known as a psychoanaleptic and stimulant without sympathomimetic effects[12].

Levophacetoperane showed good opportunities for a largescale medical practice, and, thereby, studying its effect upon nervous system is of peculiar interest. Levophacetoperane reached a level of clinical evidence unmatched by any other drug (psychotonics, stimulants or psychoanaleptic agents). Experimented in children, adolescents or adults, it is gaining increasing medical value due to its therapeutic benefit and the few secondary effects. Levophacetoperane interest was increasingly high until antipsychotic medications and other psychotropic drugs produced by the same pharmaceutical company (Rhône-Poulenc) overwhelmed the drug market in the late 1960's.

This literature review reports experimental researches and evaluations, thesis and clinical studies at least on 1821 healthy either children, or adolescents or adults patients, on a large age-range (4 to 80 years), with a wide dose-range (5 to 240 mg/d) and sometimes for a very long time of exposure, up to several years, and only between 1959 and 1967 (Table 4).

| Medical conditions, measurements | Oligophrenia, behavioral disorders, intellectual and social disabilities | Psychasthenia, apathy, depressive disorders[12,44-53] | Schizophrenia, spectrum and psychotic disorders[20,41,44-47,49,50,56,58,60-62] | Other neuropsychiatric disorders and neurological behavior[20,41,44,45,47-53,55,56,58,60,60,63] | Narcolepsy and cataplexy[48,51,64] | Healthy and control[20,39,65] |
|--|---|--|---|--|---|--|
| Clinical experiments, trials (n) | 9 open-label studies, 2 single-blind versus placebo or methylphenidate | 12 open-label studies | 10 open-label studies, 2 single-blind methylphenidate, or isocarboxa | 15 open-label, 2 single-blind studies versus methylphenidate or imipramine, phenelzine or pheniprazine | 3 open-label studies | 3 open-label studies |
| Population, hospitalized or ambulatory participants (n) | 406 children, adolescents, young adults | 583 adults | 571 adults | 156 adolescents, adults | 9 adults | 96 children, adolescents, adults |
| Age range, medium (years) | 6-23, 13 | 20-80, 35 | 20-70, 33 | 16-80, 35 | 19-57, 34 | 6-47, 25 |
| Dose range, medium (mg/d) | 5-45, 20 | 5-180, 40 | 10-240, 60 | 5-180, 45 | 5-80, 30 | 5-20, 10 |
| Duration of treatment, medium (days, weeks, months, years) | 10 days-6 months, 4 weeks | 2 weeks-14 months, 3 months | 3 weeks-2 years, 2 months | 1 week-2years, 4 months | 1 week-16 months, 12 months | 1 day-6 months, 3 weeks |
| Efficacy assessments, clinical improvement (%) | Behavioral and cognitive assessments, psychometric and speech evaluations, psychiatric observation, | Medical observation, behavioral evaluation, psychiatric assessment, much improved in | Psychiatric criteria and measurements, clinical observations, and tests symptoms evaluation and | Psychiatric criteria, assessment, psychotherapy and clinical symptomatology evolution | Clinical observation, sleepiness testing, neurologic examination and EEG measurement, | Medical examination, psychological evaluations, reaction-time, differentiation test, memorizing investigation with |

| | | | | | | |
|---|---|--|---|---|--|--|
| | mild to very much improved up to 50% in all conditions | 50-80% | EEG recordings, up to 60% globally improved | | effectiveness on alertness, sleepiness, mood, brain activity and 100% improvement on cataplexy | a significant improvement above all on attention stimulation and memory functions |
| Safety profile, adverse events (n) | Mild psychomotor instability and/or irritability in some cases, none significant adverse events | Low doses (5-20 mg/d), generally well-tolerated, none serious adverse event or death | Well-tolerated with a global improvement on negative symptoms, cognitive exhaustion or paradoxical excitation and appetite reduction reported | Well-tolerated with an improvement on various symptomatology up to 40%, agitation and anxiety in some cases at high doses | Dose-dependant anxiety, headaches, or insomnia | Speech agitation, giddiness, dizziness or slight headache in side-effect, but generally well-tolerated |

Table 4. Summary review of clinical levophacetoperane study reports in children, adolescents and adults with neuropsychiatric disorders

Levophacetoperane has been used almost as much in children as in adults and in very extensive psychiatric conditions, from mild intellectual disabilities and behavioral disorders to personality disorders (e.g. schizophrenia) and in various mood disorders with varying degrees of improvement.

Beaujard and Revol were the first psychiatrists showing that levophacetoperane had a therapeutic effect on motor hyperactivity and attention[55,66], when Labaï noted that its therapeutic action could be greater than that of methylphenidate, fully acting on attention, cognition and memory[49].

Levophacetoperane became also the preferred psychoanaleptic agent for treatment of intellectual disabilities[55,67].

The literature points out that levophacetoperane may be efficient in many psychiatric conditions with a benefit-risk balance in favor to those who are stable and treated with effective antipsychotic medications but also in untreated patients. In healthy subjects, levophacetoperane was well-tolerated at a dose-range 5-20 mg/d with a benefit on memory functioning and attention span.[65]

Clearly preferred to methylphenidate by French psychiatrists, because it led fewer side effects in children, levophacetoperane seemed efficient at low dose (5-10 mg/d), in equivalence to methylphenidate (10-20 mg/d), but can be administrated for a long time during many months compared to methylphenidate. Its benefit on behavior was generally abrupt and occurred at the beginning of the treatment; it rarely increased progressively and usually appeared after approximately two weeks[12,44,57].

Experiments in oligophrenia, behavioral disorders, intellectual and social disabilities

Oligophrenia is defined as a developmental retardation, which is associated to impairment in adaptive behavior, emotional disturbances, close to autism spectrum disorders with mental disabilities[8].

If motor manifestations of aggressiveness often gave rise to major therapeutic problems, psychotropics (e.g. neuroleptics) leading to undesirable side effects, psychostimulants were in first-line administered to oligophrenics[12,45,47].

Since Bradley[1], who found that administration of amphetamine tended to improve school performances, particularly arithmetic in one half of the children treated[68], investigated the results of thiamine (B1 vitamin) on oligophrenics. Effectiveness submitted to debatable arguments, other drugs such as glutamic acid have been studied for the treatment of oligophrenia.[69] Amphetamine and other stimulants did not increase intelligence, learning capacity, speed and accuracy of voluntary attention, fluency or memory in mental defectives, thus were abandoned for oligophrenia treatment.

A significant therapeutical effect seemed to be demonstrated on oligophrenic children, especially from a cognitive approach, and the analysis of their intellectual development has been shown a slight increase in the rapidity of development with only 5-10 mg/d of levophacetoperane[41]. In 60% of oligophrenia cases, the intelligence quotient and this improvement was maintained after treatment[48]. In terms of behavior, it increased initiative, order, method and stability. It was distinguished an immediate effect: children worked faster, better and made fewer mistakes; and a long-term effect, which boiled down to better learning possibilities compared to controls[41,56,66]. In cognitive instability, levophacetoperane improved attention in children with oligophrenia as evidenced by neuropsychological tests[41].

In adults with oligophrenia, their behavior towards work was found greatly improved by levophacetoperane, and this improvement was usually effective at the start of the treatment but generally disappeared as the treatment continued; yet, it would sometimes persist[49,50]. Levophacetoperane, differently to other stimulant agents, seemed to act on intellectual disabilities even after to be withdrawn in children with a success above 50%[39,41,57]. This aspect has never been documented with methylphenidate or amphetamines salts under the same experimental conditions.

Experiments in psychasthenia, apathy and depressive disorders

Described by Raymond and Janet in 1903[70], in order to characterize neurosis with fatigue and a sense of strangeness, a tendency towards introspection, with scruples and abulia to which can be added some changes in personality, psychasthenia could be matched to

obsessional neurosis and depression[8,71]. Psychasthenia has been previously treated using tonic solutions and stimulants. The potential therapeutic effects of amphetamine on psychasthenic patients led investigations and research development reports, but indicating that amphetamine could lead a depressive effect, its indication has not been recommended[72].

Levophaceterane has also been administrated to psychasthenic subjects, those suffering from mental adynamia and sometimes to those who did not react to antidepressants. According to the clinical observations in these studies, appetite and sleep were less impaired by levophaceterane than by amphetamine salts and levophaceterane did not lead any depressive effect rebound[52,61].

Several hundred patients, mostly adults, who did not respond to other treatments (e.g. anti-depressive agents), were put on levophaceterane and found themselves improved by this medication[45,52,73].

Only restlessness and anxiety side effects were found in psychasthenics treated by levophaceterane and were directly dose-dependent. At highest doses levophaceterane (60 mg/d) could lead to anxiety in those with a complex depressive syndrome, and an add-on neuroleptic (e.g levomepromazine) could be administrated in background. Levophaceterane in the morning was associated to levomepromazine at evening and led to a global improvement[41].

Low doses of levophaceterane (5-20 mg/d) provided a continuous benefit on depressive illness symptomatology in majority of cases with a global improvement up to 80%[12,46,48,49,53,63,73].

Experiments in schizophrenia spectrum and psychotic disorders

Increasingly clinical reviews point out the deleterious effects of amphetamine salts and methylphenidate on psychotic symptomatology and the incidence risk of psychosis in adolescents and young adults with ADHD, who were receiving stimulant prescriptions[74].

Past literature in 1950's and 1960's failed to express any potential benefit of these drugs among various psychotic conditions but reported their useful help to reverse dystonia, dyskinesia and lethargy induced by neuroleptics. More specifically, schizophrenia has been previously targeted by levophaceterane and stimulant compounds, but not as primary treatment for its symptomatology but reversal side effects of anti-psychotics[41,44,58,62].

Unlike sympathomimetics, levophaceterane did not increase blood pressure and heart rate. Its effects were therefore less compared to those of amphetamine or methylphenidate[41,61].

Schizophrenia was better treated with methylphenidate than levophaceterane when its symptomatology was mild to moderate, but a better effectiveness on social (*pragmatic*)

communication *disorder* was observed for levophacetoperane compared to methylphenidate[41].

Toxic reactions, due to levophacetoperane leading to auditory and visual hallucinations ideas of reference or paranoid delusions, have never been reported in these experiments[58,61–63].

More effective and better tolerated than methylphenidate and amphetamine in almost all the studies that were conducted, levophacetoperane obtained only mixed success on psychotic disorders and on schizophrenia, with an average success rate of 30%[41].

Experiments in narcolepsy and cataplexy

In the early 1930's, Doyle and Daniels, Janota, and Daniels described the use of ephedrine to treat sleepiness in narcolepsy. During 1930's, amphetamine salts have been introduced in narcolepsy as treatment[75–77].

The comparative action of ephedrine, amphetamines and levophacetoperane, used to treat narcolepsy and cataplexy, had to take into account the disadvantages of the sympathicomimetic effects of ephedrine and amphetamines.

The anti-cataplectic action of ephedrine, amphetamines and methylphenidate has always been much debated and that is why the action of new substances has been examined.

It has examined both the alerting and the anti-cataplectic effects of many potential drugs such as protriptyline. Prior to the introduction of sodium oxybate as an anti-cataplectic agent, there had been several studies on the efficacy of anti-cataplectic pharmacotherapies, including imipramine derivatives or MAO inhibitors.

Overall, if these drugs had a constant beneficial effect on narcolepsy cataplexy, none of them did lead to the almost complete disappearance of narcoleptic symptoms.

Garde firstly reported that levophacetoperane showed a significant benefit on narcolepsy-cataplexy in children and adults, without anxiety or any sympathicomimetic effects often caused by amphetamines. Levophacetoperane favored the intellectual effort also in duration, whilst providing tranquility and subsequently better intellectual performance[78].

The results recorded by the experiments showed that doses of levophacetoperane used were as low as 5-10 mg/d. Although the effect of the medication waned over the course of the day, it did not seem necessary to increase to more than half or one tablet in the morning and at noon to keep the subject alert[78].

As already reported, there were no addictive effects and the product could be deleted without appearing in a state of need. There was also no need to increase the doses during the course of the treatment. On the contrary, the authors had the feeling that there was awareness raising and that a down titration was acceptable, and this very unlike with amphetamines, which on the contrary, often led to drug habituation by increasing administered doses[64,78].

Levophacetoperane, enhancing ability for intellectual assignments and memory processing, improving feeling of vigor and motivation for work, has constantly proved to produce a adequate stimulating effect upon wakefulness and intellectual efficiency[39,41,65].

Conclusion

Levophacetoperane (or NLS-3) is definitively a stimulant, whose chemical structure is the reverse ester of methylphenidate and possesses different types of pharmacological effects.

On a pharmacological level, no vasoconstrictor or sympathicomimetic properties are reported, when biochemically, it releases catecholamines from the neurons and inhibits the uptake of dopamine and norepinephrine. It also is a mildly inhibitor of M₃ receptors and activator of Y₁ receptors.

Animal toxicology studies have placed levophacetoperane at the highest level of medication before methylphenidate and amphetamine.

Clinically, it has been used as an active stimulant, a mild antidepressant agent and a moderate appetite suppressant. In repeated administrations, it has never developed addictive effects and in chronic administration of increasingly higher doses, none significant psychiatric exacerbation or psychosis has been reported.

Levophacetoperane did not express any addictive effect and could be removed without inducing a need. No dose increase was necessary during the treatment duration. On the contrary, the impression was that there was rather an awareness of the product and that the doses could be decreased, constituting so an originality of this drug, differentiating it from amphetamine salts, which could give rise or leading to addictions[78].

In this exhaustive review of previous experiments, and addition of more recent studies, including almost two thousands subjects or patients, levophacetoperane (or NLS-3) appeared to be fairly robust and stable in its efficacy performances with a clear benefit in severe psychiatric disorders, including oligophrenia, psychasthenia, apathy, mood and psychotic symptomatology. It could be a first line candidate for ADHD patients with or without addiction. Above all, none of these exhaustive clinical studies showed inferiority of

levophacetoperane to methylphenidate and the benefit was always significant on inattention, perception, cognition symptomatology or psychasthenia[39,65].

Intellectual disabilities were often improved by a stimulation of selective and sustained attention, and by an increased faculty of ideation. Compared to amphetamine, there weren't any delusional behavior or abnormal mental hyperactivity. Compared to methylphenidate, the experience was better in terms of concentration and mood stability for levophacetoperane in all conditions at any time[41].

In children long-term treated by levophacetoperane, an optimal effective and well-tolerated dose identified was between 5 and 10 mg/d (equivalent for methylphenidate to a dose-range of 10-20 mg/d). A mean dose of levophacetoperane of 25 mg/d in children was always well tolerated.

Levophacetoperane showed a major clinical benefit with fewer side effects in children than methylphenidate at equivalent doses[41].

Behavioral disabilities concomitants of brain damage in these studies appeared to fall into 4 dimensions: hyperactivity, distractibility, emotional lability and inconsistency. These terms were widely employed but with little specificity and often unspecifically measured using standardized assessments or rating scales, but levophacetoperane, in large doses-range and even at low dose, obtained a major clinical benefit with few side-effects in children.

In adults, the difficulty leading to appreciate effectiveness of levophacetoperane had been in the variety of psychiatric disorders itself. In most of cases or in the group of adults tested with levophacetoperane, neuroleptics at high doses had often been administrated before and most of these patients were considered as refractory in schizophrenia, neurosis or dementia. Adults with mild depression or anxiety were often improved with levophacetoperane cures and those categorized as psychasthenics completely improved with levophacetoperane[56,58,61].

Despite this very large and exhaustive literature originated from clinical experiments and various studies, levophacetoperane was never a first choice compared to methylphenidate, even though in the same years methylphenidate never benefited from such a large number of clinical and preclinical investigations. Levophacetoperane was accepted in Canada, but behind methylphenidate. It is especially in France, more than in Europe that levophacetoperane benefited from certain reputation from neurologists and psychiatrists[8].

During the 1970's, no study using levophacetoperane was performed. According to medical experts, levophacetoperane and methylphenidate were effective and safe, yet these medications gained a negative reputation in general public and media. In France, cyclists used both drugs for increasing performances[79]. Urinary or blood tests detecting

amphetamines were not reliable, and many athletes were found negative, even though they have consumed them. Unlike amphetamine, which was easily detectable, levophacetoperane like methylphenidate seemed to be difficult in detecting as requiring complicated detection methods failing to be systematically used[80].

Psychostimulants gradually became less prescribed in France, also because neurobehavioral disorders were rarely diagnosed and inattention, impulsivity and hyperactivity symptoms unfortunately treated with neuroleptics or other psychotropics.

For this reason, in France, these products have been withdrawn commercially whilst amphetamine remained authorized and present on the drug market until 1990's.

When none published study or toxicology report led to the conclusion that levophacetoperane or methylphenidate were inappropriately administrated in France or leading to adverse events, they were withdrawn from the market for commercialized reasons[8].

References

- [1] Bradley, C. The Behavior of Children Receiving Benzedrine. *AJP*, **1937**, *94*, 577–585.
- [2] Cortese, S.; Adamo, N.; Del Giovane, C.; Mohr-Jensen, C.; Hayes, A.J.; Carucci, S.; Atkinson, L.Z.; Tessari, L.; Banaschewski, T.; Coghill, D.; Hollis, C.; Simonoff, E.; Zuddas, A.; Barbui, C.; Purgato, M.; Steinhausen, H.-C.; Shokraneh, F.; Xia, J.; Cipriani, A. Comparative Efficacy and Tolerability of Medications for Attention-Deficit Hyperactivity Disorder in Children, Adolescents, and Adults: A Systematic Review and Network Meta-Analysis. *Lancet Psychiatry*, **2018**, *5*, 727–738.
- [3] Wigal, T.L.; Newcorn, J.H.; Handal, N.; Wigal, S.B.; Mulligan, I.; Schmith, V.; Konofal, E. A Double-Blind, Placebo-Controlled, Phase II Study to Determine the Efficacy, Safety, Tolerability and Pharmacokinetics of a Controlled Release (CR) Formulation of Maziadol in Adults with DSM-5 Attention-Deficit/Hyperactivity Disorder (ADHD). *CNS Drugs*, **2018**, *32*, 289–301.
- [4] Nageye, F.; Cortese, S. Beyond Stimulants: A Systematic Review of Randomised Controlled Trials Assessing Novel Compounds for ADHD. *Expert Rev Neurother*, **2019**, *19*, 707–717.
- [5] Polanczyk, G.; de Lima, M.S.; Horta, B.L.; Biederman, J.; Rohde, L.A. The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis. *Am J Psychiatry*, **2007**, *164*, 942–948.
- [6] Posner, J.; Polanczyk, G.V.; Sonuga-Barke, E. Attention-Deficit Hyperactivity Disorder. *Lancet*, **2020**, *395*, 450–462.
- [7] Thorpy, M.J.; Hiller, G. The Medical and Economic Burden of Narcolepsy: Implications for Managed Care. *Am Health Drug Benefits*, **2017**, *10*, 233–241.
- [8] Konofal, É.; Dolitsky, D. *ADHD and Its Medications, an Illustrated History Over Time; Impulsion naturelle*, **2019**.
- [9] Morton, W.A.; Stockton, G.G. Methylphenidate Abuse and Psychiatric Side Effects. *Prim Care Companion J Clin Psychiatry*, **2000**, *2*, 159–164.
- [10] Conners, C.K.; Eisenberg, L. The Effects of Methylphenidate on Symptomatology and Learning in Disturbed Children. *Am J Psychiatry*, **1963**, *120*, 458–464.
- [11] Cortese, S.; Holtmann, M.; Banaschewski, T.; Buitelaar, J.; Coghill, D.; Danckaerts, M.; Dittmann, R.W.; Graham, J.; Taylor, E.; Sergeant, J.; European ADHD Guidelines Group. Practitioner Review: Current Best Practice in the Management of Adverse Events during Treatment with ADHD Medications in Children and Adolescents. *J Child Psychol Psychiatry*, **2013**, *54*, 227–246.
- [12] Sivadon, P.; Chanoit; Azoulay. Premiers Résultats Cliniques de l'emploi d'un Nouveau Psycho-Tonique. Le 8228 R.P. *Annales Médico-psychologiques*, **1959**, *tome II*, 536–537.
- [13] Konofal, E.; Figadere, B. *Phacetoperane Pour Traiter Un Trouble Deficit de l'attention Hyperactivite*; Google Patents, **2016**.
- [14] Thai, D.L.; Sapko, M.T.; Reiter, C.T.; Bierer, D.E.; Perel, J.M. Asymmetric Synthesis and Pharmacology of Methylphenidate and Its Para-Substituted Derivatives. *J Med Chem*, **1998**, *41*, 591–601.
- [15] Nahm, S.; Weinreb, S.M. N-Methoxy-n-Methylamides as Effective Acylating Agents. *Tetrahedron Letters*, **1981**, *22*, 3815–3818.
- [16] Dargazanli, G.; Estienne-Bouhtou, G.; Marabout, B.; Roger, P.; Sevrin, M. N-Phenyl(Piperidin-2-Yl)Methyl]Benzamide Derivatives, Preparation Thereof, and Use Thereof in Therapy. EP1527048A2, May 4, **2005**.
- [17] Dewar, G.H.; Parfitt, R.T.; Sheh, L. ChemInform Abstract: Stereochemical features of reduction and elimination reactions of 8-methyl-6-phenyl-8-azabicyclo(3.2.1)oct-6-ene (6-phenyl-6-tropene). *Chemischer Informationsdienst*, **1985**, *16*.
- [18] Pham, V.C.; Charlton, J.L. Methyl (S)-Lactate as a Chiral Auxiliary in the Asymmetric Synthesis of Bao Gong Teng A. *J. Org. Chem.*, **1995**, *60*, 8051–8055.
- [19] Laboratoires Specia. *Lidépran : psycho-actif Lidépran*; Laboratoires Specia: Paris, **1963**.
- [20] Ziolk, H.U. [The significance of psychodynamic factors for the effect of

- phenylpiperidylcarbinol (Bayer 1313)]. *Med Exp Int J Exp Med*, **1960**, 2, 224–227.
- [21] Michel, J.R.; Marie, J.N. New Esters. US2928835A, March 15, **1960**.
- [22] Ramirez, A.; Vial, H.; Barailler, J.; Pacheco, H. [Effects of levophacetoperane, pemoline, fenozolone, and centrophenoxine on catecholamines and serotonin uptake in various parts of the rat brain]. *C R Acad Hebd Seances Acad Sci D*, **1978**, 187, 53–56.
- [23] Snyder, S.H.; Coyle, J.T. Regional Differences in H3-Norepinephrine and H3-Dopamine Uptake into Rat Brain Homogenates. *J Pharmacol Exp Ther*, **1969**, 165, 78–86.
- [24] Hanna, C.; Upton, P.D.; Chambers, W.F. Comparative Effects of D-1 Amphetamine and 1-Phenyl-1-(Piperidyl-2')-1-Acetoxy-1-Methane (R.P. 8228) in Antagonizing Barbiturate Hypnosis. *Archives internationales de pharmacodynamie et de therapie*, **1963**, 145, 553–564.
- [25] Cheng, Y.; Prusoff, W.H. Relationship between the Inhibition Constant (K₁) and the Concentration of Inhibitor Which Causes 50 per Cent Inhibition (I₅₀) of an Enzymatic Reaction. *Biochem Pharmacol*, **1973**, 22, 3099–3108.
- [26] Zlotos, D.P.; Bender, W.; Holzgrabe, U. Muscarinic Receptor Agonists and Antagonists. *Expert Opinion on Therapeutic Patents*, **1999**, 9, 1029–1053.
- [27] Schenk, S. Sensitization to Cocaine's Reinforcing Effects Produced by Various Cocaine Pretreatment Regimens in Rats. *Pharmacology Biochemistry and Behavior*, **2000**, 66, 765–770.
- [28] Schenk, S.; Partridge, B.; Shippenberg, T.S. U69593, a Kappa-Opioid Agonist, Decreases Cocaine Self-Administration and Decreases Cocaine-Produced Drug-Seeking. *Psychopharmacology (Berl)*, **1999**, 144, 339–346.
- [29] Schenk, S.; Partridge, B.; Shippenberg, T.S. Reinstatement of Extinguished Drug-Taking Behavior in Rats: Effect of the Kappa-Opioid Receptor Agonist, U69593. *Psychopharmacology (Berl)*, **2000**, 151, 85–90.
- [30] Schenk, S.; Partridge, B. Cocaine-Seeking Produced by Experimenter-Administered Drug Injections: Dose-Effect Relationships in Rats. *Psychopharmacology (Berl)*, **1999**, 147, 285–290.
- [31] Morani, A.S.; Kivell, B.; Prisinzano, T.E.; Schenk, S. Effect of Kappa-Opioid Receptor Agonists U69593, U50488H, Spiradolone and Salvinorin A on Cocaine-Induced Drug-Seeking in Rats. *Pharmacol Biochem Behav*, **2009**, 94, 244–249.
- [32] Spangler, R.; Zhou, Y.; Maggos, C.E.; Schlussman, S.D.; Ho, A.; Kreek, M.J. Prodynorphin, Proenkephalin and Kappa Opioid Receptor mRNA Responses to Acute "Binge" Cocaine. *Brain Res Mol Brain Res*, **1997**, 44, 139–142.
- [33] Wee, S.; Koob, G.F. The Role of the Dynorphin-Kappa Opioid System in the Reinforcing Effects of Drugs of Abuse. *Psychopharmacology (Berl)*, **2010**, 210, 121–135.
- [34] Groer, C.E.; Tidgewell, K.; Moyer, R.A.; Harding, W.W.; Rothman, R.B.; Prisinzano, T.E.; Bohn, L.M. An Opioid Agonist That Does Not Induce Mu-Opioid Receptor--Arrestin Interactions or Receptor Internalization. *Mol Pharmacol*, **2007**, 71, 549–557.
- [35] Kivell, B.M.; Ewald, A.W.M.; Prisinzano, T.E. Salvinorin A Analogs and Other κ -Opioid Receptor Compounds as Treatments for Cocaine Abuse. *Adv Pharmacol*, **2014**, 69, 481–511.
- [36] Simonson, B.; Morani, A.S.; Ewald, A.W.M.; Walker, L.; Kumar, N.; Simpson, D.; Miller, J.H.; Prisinzano, T.E.; Kivell, B.M. Pharmacology and Anti-Addiction Effects of the Novel κ Opioid Receptor Agonist Mesyl Sal B, a Potent and Long-Acting Analogue of Salvinorin A. *Br J Pharmacol*, **2015**, 172, 515–531.
- [37] Butelman, E.R.; Kreek, M.J. Discriminative Stimulus Properties of Opioid Ligands: Progress and Future Directions. *Curr Top Behav Neurosci*, **2018**, 39, 175–192.
- [38] Courvoisier, S. Étude Des Propriétés Stimulantes Centrales de l'Acétoxy-l-Phényl-l-(Pipéridyl-2')-l-Méthane, Threo, Levogyre (8228 R. P.). *Annales Médico-psychologiques*, **1959**, 117, 345.
- [39] Fournier Michel. *Contribution à l'étude Des Effets Du Lidepran En Neuro-Psychiatrie Infantile*, Faculté de Médecine de Paris: Paris, **1962**.
- [40] Dobkin AB. Drugs Which Stimulate Affective Behavior. 2. Comparison of the Analeptic Effect of d'amphetamine, Bemigrade with Amiphenazole, Methylphenidylacetate, Iproniazid (Micoren) and RP8228. *Anaesthesia*, **1960**, 15, 146–153.
- [41] Bontronc, C.; Médecine, U. de P. (1896-1968) F. de. *A Propos Des Psychotoniques*

Levophacétopérane et Méthylphénidate Dans Les Psychoses et Dans Les États Psychonévrotiques Mineurs; R. Vezin, **1961**.

[42] Salinger, R.-J. *Contribution à l'étude Expérimentale Des Nouvelles Médications Psychoactives et Leur Utilisation Thérapeutique En Psychiatrie: A Propos de l'une d'elles: Le 8228 RP Ou Chlorhydrate de Phényl-1 (Pipéridyl-2) 1-Acétoxy-Méthane Thréolévogyre*; **1961**.

[43] Jean-Charles Bizot; Trovero, F.; Figadere, B.; Akagah, B.; Konofal, E. Examination of Potential Addictive Effects of NLS-3, a New Compound in Development for ADHD - 4th. EUNETHYDIS International Conference on ADHD, Berlin, Germany, 16th-19th October 2016. **2016**.

[44] Sivadon, P.; Salinger, R.J.; Quidu, M. Résultats Cliniques de l'emploi En Psychiatrie d'un Nouveau Psychotonique: Le 8228 RP (A Propos Des 134 Premières Observations). *Comptes rendus des séances de l'Académie des Sciences (Paris)*, **1960**, 760–769.

[45] Sivadon, P.; Salinger René. [Clinical study of a new psychoactive drug in psychiatry, RP-8228 or threo-levo-1-phenyl-1-(2-piperidyl)-1-acetoxymethane HCl]. *Annales Médico-psychologiques*, **1962**, 120, 824–832.

[46] Chanoit, P.-F. Quelques Considérations Sur l'utilisation Psychothérapeutique d'un Nouveau Psychotonique. *Annales Médico-psychologiques*, **1960**, 118, 869–878.

[47] Follin, S.; Chanoit, P.-F.; Huchon, J. L'emploi d'un Nouveau Psychotonique : Le 8228 RP. En Milieu Hospitalier (Bilan Effectué Après Deux Ans d'essais). *Comptes rendus des séances de l'Académie des Sciences (Paris)*, **1970**, 770–776.

[48] Guyotat, J.; Hochmann, J. [The present status of RP-8228 in psychiatric therapeutics. Apropos of 32 recent cases]. *Lyon Med*, **1962**, 94, 777–783.

[49] Labaï, C. *Résultats cliniques et remarques retirés de l'emploi de l'iproniazide, du RP 82-28 et du nialamide en milieu hospitalier psychiatrique départemental*, Impr. du Sud-Ouest: Toulouse, **1961**.

[50] Oules, J.; Labaï, C. Thérapeutique. Sujets Libres : Indications et Emploi d'un Nouveau Psychotonique : Le 8228 RP. *Comptes-rendus du Congrès de Psychiatrie et de Neurologie de langue française. Lille*, **1960**, 859.

[51] Garde, A. Résultats obtenus avec le 8.228 R.P. après deux ans d'utilisation de ce psychotonique. *Lyon Med*, **1962**, 94, 1549–1555.

[52] Deshaies, G.; Fontaine, C.; Spelz, M.T. [Use of a psychotonic in psychiatry]. *Ann Med Psychol (Paris)*, **1965**, 123, 630–637.

[53] Grimberg, L.; Grimberg-Pivet, S. Psychiatrie. Thérapeutique. Intervention : Réflexions Sur l'utilisation Clinique Du 8228 RP. Ou Lévo-phacétopérane (Lidépran). *Comptes-rendus du Congrès de Psychiatrie et de Neurologie de langue française. Lausanne. Tome I*, **1965**, 812.

[54] Faure, H.; Faure, M.L. Les Apports Du Nozinan En Neuro-Psychiatrie Infantile (Levomépromazine, 70.44. RP.). In: *Psychological and Sociological Problems in Imbecility*; Karger Publishers, **1963**; pp. 160–164.

[55] Beaujard M; Revol E. [Clinical tests of the activity of RP 8228 (phacetoperane) in an oligophrenic child]. *Pédiatrie*, **1960**, 15, 310–316.

[56] Guyotat, J.; Beaujard, M.; Guillaumin, J. Evaluation Psychométrique Des Effets d'un Psychotonique, Le 8.228R.P. Considérations Méthodologiques. Communication Au Collège Neuro-Psychopharmacologique, Bâle, 4-7 Juillet 1960. *Neuro-pharmacology*, **1961**, 2, 361–370.

[57] Beaujard, M. Phacetoperane in Mental Retardation of Children. *Experta Medica (International Congress Series)*, **1960**, 100.

[58] Bellander-Löfvenberg, S.; Osterman, E.; Brattemo, C. RP-8228—Ett Nytt Psykoanalepticum. *Nordisk Psykiatrisk Tidsskrift*, **1961**, 15, 141–147.

[59] Penteado Bueno, U.; Capp, A.B. Resultados Clínicos (Conseqüentes Ao Emprêgo de Um Novo Psicotônico Em Menores Oligofrênicos e Epilépticoe Oligofrênicos. *O Hospital*, **1962**, 1003–1017.

[60] Sivadon, P.; Chanoit, P.-F.; Azoulay, J. Premiers Résultats Cliniques de l'emploi d'un Nouveau Psychotonique, Le 8228 R.P. [First Clinical Results with a New Psychotonic, RP

8228.]. *Méd. Psychol., séance du*, **1959**, 117, 536–541.

[61] Ban, T.A.; St Laurent, J. The Stimulating Effect of RP 8228 on Inactive Psychiatric Patients. *J Neuropsychiatry*, **1961**, 3, 91–95.

[62] Brattemo, C.-E. Experimentalpsykologisk Undersökning Med Ett Psykotonicum, R P.-8228. *Nordisk Psykiatrisk Tidsskrift*, **1961**, 15, 147–154.

[63] Leitch, A.; Seager, C.P. A Trial of Four Anti-Depressant Drugs. *Psychopharmacologia*, **1963**, 4, 72–77.

[64] Devic, M.; Revol, M.; Michel, F. A Propos of the Treatment of Narcolepsy: Trial Use of a New Psychoactive Agent, RP 8228. *Lyon medical*, **1962**, 94, 1557–1562.

[65] Joncev, V.; Stefanova, E. Investigations on Levophacetoperan Effect upon Higher Nervous Activity and Memory. *Folia medica*, **1967**, 9, 368–372.

[66] Beaujard, M. Le Phacétopérane Dans l'arriération Mentale Chez l'enfant. In: **1963**; pp. 165–167.

[67] Faure, H.; Faure, M.L.; Stoppa, I. Les Effets Activateurs Du Phacétopérane En Neuropsychiatrie Infantile. *Revue de Neuropédiatrie Infantile et d'Hygiène Mentale de l'Enfance*, **1962**, 10, 7–8.

[68] Cutler, M.; Little, J.; Strauss, A. The Effect of Benzedrine on Mentally Deficient Children. *Am J Ment Defic*, **1940**, 45, 59–65.

[69] Morris, J.V.; Macgillivray, R.C.; Mathieson, C.M. The Results of the Experimental Administration of Amphetamine Sulphate in Oligophrenia. *Journal of Mental Science*, **1955**, 101, 131–140.

[70] Raymond, F.; Janet, P. *Les Obsessions et La Psychasthénie*; F. Alcan: Paris, **1903**; Vol. tome 2.

[71] Pitman, R.K. Janet's Obsessions and Psychasthenia: A Synopsis. *Psychiatr Q*, **1984**, 56, 291–314.

[72] Hubin, P.; Servais, J. [Study on the effects of amphetamine on human personality]. *Psychopharmacologia*, **1968**, 12, 239–249.

[73] Sutter, J.M.; Delpretti, G.M. Le Lévo-phacétopérane (Lidépran) En Thérapeutique Psychiatrique. *Sud Med Chir*, **1962**, 998–1005.

[74] Fluyau, D.; Mitra, P.; Lorthe, K. Antipsychotics for Amphetamine Psychosis. A Systematic Review. *Front Psychiatry*, **2019**, 10, 740.

[75] Doyle, J.B.; Daniels, L.E. Narcolepsy; Results of Treatment with Ephedrine Sulphate. *JAMA*, **1932**, 98, 542–545.

[76] Yoss, R.E.; Daly, D. Treatment of Narcolepsy with Ritalin. *Neurology*, **1959**, 9, 171–173.

[77] Janota, O. [Thérapeutique de La Narcolepsie Par l'éphédrine] In: Proceedings of the Compte-rendu des travaux de la section Neuro-Psychiatrique du 14e congrès des médecins et naturalistes polonais; Poznan, **1933**.

[78] Garde, A. Résultats Obtenus Avec Le 8.228 R.P. Après Deux Ans d'utilisation de Ce Psychotonique. *Lyon médical*, **1962**, 1549–1555.

[79] Mondenard, J. Dopage: Les Pipéridines: Lidépran, Mératran, Ritaline. Des Bricoles sans Grands Effets. *Médecine du sport*, **1991**, 65, 00145–00148.

[80] Delbeke FT; Debackere M. Isolation and Detection of Methylphenidate, Phacetoperane and Some Other Sympatomimetic Central Nervous Stimulants with Special Reference to Doping. I. Gas Chromatographic Detection Procedure with Electron Capture Detection for Some Secondary Amines. *Journal of chromatography*, **1975**, 106, 412–417.

Acknowledgements

The authors would like to thank Eurofins (formerly Cerep), Poitiers, France, for their assistance in the assay techniques. The authors wish to state that the material presented in this review reflect only their views and not necessarily those of the NLS Pharmaceuticals.

Conflict of interest statement

The authors declare that there is no conflict of interest except for Dr Figadère and Dr Konofal who declare to be consultants for NLS Pharmaceuticals, Stans, Suisse and to be inventor for patent granted: Phacetoperane for the treatment of attention-deficit hyperactivity disorder

<https://patents.google.com/patent/EP2785344B1>

Funding

Part of this research was funded by NLS Pharmaceuticals, Zurich, Suisse.