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Piracetam and Piracetam-Like Drugs

From Basic Science to Novel Clinical Applications to CNS Disorders

Andrei G. Malykh and *M. Reza Sadaie*

NovoMed Consulting, Silver Spring, Maryland, USA

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Abstract

There is an increasing interest in nootropic drugs for the treatment of CNS disorders. Since the last meta-analysis of the clinical efficacy of piracetam, more information has accumulated. The primary objective of this systematic survey is to evaluate the clinical outcomes as well as the scientific literature relating to the pharmacology, pharmacokinetics/pharmacodynamics, mechanism of action, dosing, toxicology and adverse effects of marketed and investigational drugs. The major focus of the literature search was on articles demonstrating evidence-based clinical investigations during the past 10 years for the following therapeutic categories of CNS disorders: (i) cognition/memory; (ii) epilepsy and seizure; (iii) neurodegenerative diseases; (iv) stroke/ischaemia; and (v) stress and anxiety.

In this article, piracetam-like compounds are divided into three subgroups based on their chemical structures, known efficacy and intended clinical uses. Subgroup 1 drugs include piracetam, oxiracetam, aniracetam, pramiracetam and phenylpiracetam, which have been used in humans and some of which are available as dietary supplements. Of these, oxiracetam and aniracetam are no longer in clinical use. Pramiracetam reportedly improved cognitive deficits associated with traumatic brain injuries. Although piracetam exhibited no long-term benefits for the treatment of mild cognitive impairments, recent studies demonstrated its neuroprotective effect when used during coronary bypass surgery. It was also effective in the treatment of cognitive disorders of cerebrovascular and traumatic origins; however, its overall effect on lowering depression and anxiety was higher than improving memory. As add-on therapy, it appears to benefit individuals with myoclonus epilepsy and tardive dyskinesia. Phenylpiracetam is more potent than piracetam and is used for a wider range of indications. In combination with a vasodilator drug, piracetam appeared to have an additive beneficial effect on various cognitive disabilities. Subgroup 2 drugs include levetiracetam, seletracetam and brivaracetam, which demonstrate antiepileptic activity, although their cognitive effects are unclear. Subgroup 3 includes piracetam derivatives with unknown clinical efficacies, and of these nefiracetam failed to improve cognition in post-stroke patients and rolipram is currently in clinical trials as an antidepressant. The remaining compounds of this subgroup are at various preclinical stages of research.

The modes of action of piracetam and most of its derivatives remain an enigma. Differential effects on subtypes of glutamate receptors, but not the GABAergic actions, have been implicated. Piracetam seems to activate calcium influx into neuronal cells; however, this function is questionable in the light of findings that a persistent calcium inflow may have deleterious impact on neuronal cells. Although subgroup 2 compounds act via binding to another neuronal receptor (synaptic vesicle 2A), some of the subgroup 3 compounds, such as nefiracetam, are similar to those of subgroup 1. Based on calculations of the efficacy rates, our assessments indicate notable improvements in clinical outcomes with some of these agents.

Piracetam (pyrrolidone acetamide) and related small molecule ligands share a five-carbon oxopyrrolidone ring, also referred to as racetams, belong to the class of nootropic compounds in a broader definition. The term 'nootrope' (from the Greek words *noos* for mind and *tropein* for towards) was proposed initially when a positive effect of piracetam on cognitive improvement was demonstrated.[1] Piracetam and piracetam-like drugs are modulators of cerebral functions. These agents are also used in efforts to restore memory and brain performance in patients with encephalopathies of various aetiologies, including cranial traumas, inflammation and stroke/ischaemia complications after bypass surgery, while some derivatives are indicated for neurological disorders such as seizures and neuromuscular convulsions.

The need for new medications for age-related CNS problems will increase in the near future as the generation of baby boomers approach retirement age. Memory loss is one of the major factors affecting the everyday living activities of the elderly population. Since the discovery of piracetam in the late 1960s, more than a dozen lead piracetam-like substances have been synthesized and proposed for treatment of cognitive impairment and CNS disorders.

The aim of this review is to summarize the (i) status of marketed piracetam-like drugs; (ii) data on the known chemical structures and their crucial pharmacological properties; and (iii) current trend and validity of clinical observations regarding the effects of piracetam-like compounds on brain performance and cognition. The major questions addressed in this article are: (i) what is the literature trend toward lead clinical candidate compounds in terms of potency and target specificity?; (ii) do improvements in design of new-generation chemical entities translate to improved clinical efficacy?; and (iii) do the expanded indications for the first-generation compounds exhibit any meaningful patient benefits? To determine the major trends in this field, we have surveyed the strength of associations between known mechanisms of drug action, findings in animal test systems and their relevance to clinical trial outcomes. We have compiled, tabulated and analysed clinical findings, and discuss the advantages and limitations of old- and new-generation piracetam-like compounds, and potential relevant areas that require further research.

1. Therapeutic Applications and Publications

Numerous broad clinical applications are attributed to piracetam,[2] many of which are based on open-label and/or non-controlled studies in animals and humans. Piracetam and its analogues have been used for various therapeutic interventions relating to the CNS, including (i) cognition/memory; (ii) epilepsy and seizure; (iii) neurodegenerative diseases; (iv) stroke/ischaemia; and (v) stress and anxiety.

Piracetam-related compounds have been extensively researched and large numbers of publications reported in the past 3 decades. From more than a dozen new products, eight have entered clinical investigations for various CNS indications in recent years. We searched the US national clinical trials databank,[3] PubMed and the Internet. The search criteria for clinical data in PubMed were 'clinical trial' and the tag term 'title/abstract'. The total number of clinical publications representing all compounds exceeds 300. While most papers on piracetam were published more than 10 years ago, the highest number in the past 3 years concern levetiracetam. To highlight these trends better, we tabulated the search results to indicate the numbers, sequence and continuity. Table I shows both ascending and descending number of articles for the indicated periods. Two reviews describe meta-analyses: one on efficacy of piracetam in cognitive impairment,[4] and the other on piracetam and piracetam-like compounds in experimental stroke in animals.[5] The PubMed search for phenylpiracetam, only with its trade name (Phenotropil®), retrieved

Table I. Number of clinical trial publications on piracetam-related ligands[a]

Products	3 y (2007–2009)	3 y (2004–2006)	5 y (1999–2003)	>10 y (prior to 1999)
Levetiracetam	98	70	35	2
Piracetam	10	3	18	118
Phenylpiracetam	5	3		
Brivaracetam	3			
Nefiracetam	2			
Fasoracetam			1	
Oxiracetam				22
Rolipram	1			10
Pramiracetam				4
Aniracetam				6
Nebracetam				3

a PubMed was searched with the indicated time limits and keywords, including the product names and other used names phenotropil, phenotropyl, WEB 1881 FU, NS 105, LAM 105 and MKC-231 (last accessed on 23 January 2010).

eight articles, of which six were clinical trials in patient with neurological disorders. Several selected publications on phenylpiracetam that we cite here are from Russian journals, which are not in PubMed. We reviewed, without a selection bias, key and core articles that demonstrate evidence-based clinical investigations and other available information on marketed products, clinical findings, non-clinical biochemical and pharmacological data, and promising piracetam-like drugs with unknown benefit-risk profiles.

2. Marketed Products

There are six relevant medications on the market worldwide (table II). Piracetam and levetiracetam were developed by UCB Pharma, Belgium; oxiracetam by ISF, Italy; aniracetam by Roche Pharmaceuticals, Switzerland; pramiracetam by Warner-Lambert, USA;[6] and phenylpiracetam by the Medical-Biological Institute of the Russian Academy of Sciences (manufactured by Valenta Pharmaceuticals, Russia). The product insert (International Anti-Aging Systems, UK) states that oxiracetam is for "mental syndromes caused by cerebral insufficiency, disturbances in mental performance in the elderly, and no adverse interactions have been noted", but it is unavailable from this supplier. In 2003, the State Pharmacological Committee of Russia approved phenylpiracetam as a prescription drug for cerebrovascular deficiency, depression, apathy, attention and memory decline, and it is recommended for cosmonauts for increasing physical and mental/cognitive activities in space.[7] Levetiracetam was initially approved in the US in 1999 as adjunctive therapy for partial onset seizures in adults and children aged ≥4 years, and for adults and adolescents with myoclonic epilepsy. The European Medicines Agency recently approved it as monotherapy for partial seizures and as adjunctive therapy for tonic-clonic seizures. With the exception of levetiracetam, these products are not registered as ethical medications in the US.

3. Mechanisms of Action

The pharmacology of piracetam-related drugs has been less explored than the clinical applications

Table II. Marketed piracetam-like drug products and dietary supplements[a]

Active compound	Trade name	Indication(s)	Availability		Adverse effects
			R_x	non-R_x	
Piracetam	Nootropil® Nootrop™ Nootropyl™	Neurocognitive impairments, memory decline, cortical myoclonus	Tablet/injectable (EU)	Capsule	Sleep disturbance, diarrhoea (uncommon)
Piracetam + cinnarizine	Fezam®	Cerebral circulation disorders	Capsule (Bulgaria, Russia)		Irritation, dyspepsia, headache
Oxiracetam	Neuromet®	Aging mental impairments		Capsule	Psychomotor excitability, sleep disorders
Aniracetam	Ampamet® Draganon® Sarpul®	Memory decline, neurodegenerative disorders		Tablet	Agitation, anxiety, restlessness, insomnia
Pramiracetam	Neupramir® Pramistar®	Aging mental impairments, anxiety		Tablet	Insomnia, dysphoria, gastralgia, heartburn
Phenylpiracetam	Phenotropil®	Mental function impairment CNS, neurotic disorders	Tablet (Russia)		Sleep disturbance
Levetiracetam	Keppra®	Epilepsy	Tablet/injectable (EU, USA)		Somnolence, fatigue, coordination difficulties, behavioural abnormalities

a R_x and non-R_x dose forms of the marketed piracetam-like compounds, their indications/claimed therapeutic areas, and probable, common and/or generally mild adverse effects are summarized from information provided in manufacturers' package inserts/product labels. Non-R_x forms are available from online sources.

Non-R_x = non-prescription; **R_x** = prescription.

of these drugs and remains to be elucidated. These compounds interact with target receptors in brain and modulate the excitatory and/or inhibitory processes of neurotransmitters, neurohormones and/or post-synaptic signals. The effect(s) on signal trafficking can have an impact on cognition and neurological behaviours. Several groups have suggested the roles of piracetam in energy metabolism, including (i) increased oxygen utilization in the brain, and permeability of cell and mitochondrial membranes to intermediaries of the Krebs cycle;[8,9] and (ii) synthesis of cytochrome b5.[10] These actions are possibly downstream consequences of piracetam on ion channels and/or ion transporters in neurons (see later this section).

The similarity of its chemical structure to a cyclic derivative of GABA suggests that piracetam probably has a GABA-mimetic action.[11] To date, this mechanism remains unclear. Others have proposed that it functions as an antioxidant/neurotonic[12,13] and increases the density of acetylcholine receptor.[14] Comparative and compelling data for these potential functions are unavailable. It is also unclear how piracetam exerts its broad clinical benefits through these actions. Because of differences among piracetam derivatives (table III, figure 1), it is unlikely that all these drugs will operate in a similar manner, use the same cell type(s) or drug target(s), or both. For that matter, their pharmacokinetics, degradation kinetics, fate of metabolites, and even ADMET (adsorption, distribution, metabolism, excretion and toxicity) properties, can vary. These variations can be quite profound when the studies use different test systems.

It is reasonable to expect that the compounds with 'minimal' changes in their chemical structures share the same mechanism of action, such as binding to or modulating a selective subset of neurotransmitter receptors. The following hypotheses focus on modulation of ionotropic, ligand-gated and/or voltage-dependent ion channels, such as $[Na^+/Ca^{2+}]/K^+$ exchanger pumps in neuronal cell membranes or neuromuscular junctions.

The subgroup 1 agents piracetam, oxiracetam and aniracetam (table III, figure 1) activate α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-type glutamate receptors but not kainate or NMDA receptors in neuronal cultures. This action increases the density of receptor binding sites for AMPA and calcium uptake,[38] presumably resulting in elevation of intracellular calcium ($[Ca^{2+}]i$). Pramiracetam increases the rate of sodium-dependent high-affinity choline uptake in rat hippocampal synaptosomes *in vitro*, suggesting that its effect on cognitive functions might occur via acceleration of cholinergic neuronal impulse flow in the septal-hippocampal region.[39] The affinity of phenylpiracetam to the nicotinitic acetylcholine (nACh) receptor, but not the glutamate NMDA subtype, was demonstrated in ligand-binding experiments *in vitro*. However, injection of this drug (100 mg/kg, intraperitoneally) to rats increases the numbers of both nACh and NMDA receptors, but decreases serotonin and dopamine receptors in the brain tissue.[40]

For subgroup 2 drugs (table III, figure 1), more recent data assert that levetiracetam probably acts through an alternative mechanism for its antiepileptic activity. At a therapeutic dose range, it was initially shown to decrease incoming ions in AMPA- and kainite-induced currents in cultured cortical neurons.[41] In contrast to subgroup 1 compounds, levetiracetam apparently inhibits neuronal Ca^{2+} ion channels that are possibly important to its antiepileptic effect.[41-43] In a different experimental setting using a seizure model in mice, it was later demonstrated to bind to synaptic vesicle 2A (SV2A) protein in brain membranes and fibroblasts.[44] The data correlated with the clinical application of levetiracetam as an antiepileptic drug (AED).[44] Brivaracetam and seletracetam, the newer-generation chemical entities after levetiracetam, bind to SV2A with a higher affinity and are currently being evaluated clinically for their antiepileptic properties.[23,24] It is unclear whether subgroup 2 drugs affect other physiological (nonpathological) roles of SV2A and/or disturb the normal homeostasis of calcium in different regions of brain. It is unlikely that only one mechanism of action is operative *in vivo*, allowing a selective pharmacological advantage to these drugs considering the closeness of their molecular structures

Table III. Pharmacological properties of piracetam-like compounds

Category	Active compound	IUPAC name	Potency[a] (dosage)	Bioavailability (%)[b]	Half-life[b]	References
Subgroup 1: cognitive enhancers	Piracetam	2-oxo-1-pyrrolidineacetamide	Low: 50 to >300 mg/kg/d (up to 37 g/d)	~100	4–5 h	6[c]
	Oxiracetam	2-(4-hydroxy-2-oxopyrrolidin-1-yl)acetamide	Medium: 25–40 mg/kg/d (up to 2.4 g/d)	~75	3–6 h	6,15
	Pramiracetam	N-[2-(dipropan-2-ylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide	Medium: 10–20 mg/kg/d (1.2 g/d)	~100	2–8 h	6,16,17
	Aniracetam	1-[(4-methoxybenzoyl)]-2-pyrrolidinone	Medium: 12–25 mg/kg/d (1.5 g/d)	~11	1–2.5 h	6,18
	Phenylpiracetam	2-(4-phenyl-2-oxopyrrolidin-1-yl)acetamide	High: 2.5–5 mg/kg/d (up to 0.75 g/d)	~100	3–5 h	19,20[c]
Subgroup 2: antiepileptic drugs	Levetiracetam	(2S)-2-(2-oxopyrrolidin-1-yl)butanamide	Medium: 20–60 mg/kg/d (up to 3 g/d)	~100	6–8 h	6[c]
	Brivaracetam	(2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide	Medium: 10–25 mg/kg/d (up to 1.4 g/d)	~90	7–8 h	21,22
	Seletracetam	(2S)-2-[(4R)-4-(2,2-difluoroethenyl)-2-oxo-pyrrolidin-1-yl]butanamide	High: 0.03–10 mg/kg/d (up to 0. 6 g/d)	>90	8 h	23,24
Subgroup 3: unknown clinical efficacy	Nefiracetam	N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide	Medium: 10–15 mg/kg/d (up to 0.9 g/d)	NA	3–5 h	25,26
	Nebracetam	4-(aminomethyl)-1-benzyl-pyrrolidin-2-one	Medium: 200–800 mg/d	NA	NA	27,28
	Rolipram	4-(3-cyclopentyloxy-4-methoxy-phenyl)pyrrolidin-2-one	High: 0.75–3.0 mg/d	>70	2 h	29,30
	Fasoracetam (NS-105)	(5R)-5-(piperidine-1-carbonyl) pyrrolidin-2-one	High: 100 mg/d)	79–97	4–6.5 h	31,32
	Coluracetam (MKC-231)	N-(2,3-dimethyl-5,6,7,8- tetrahydrofuro[2,3-b] quinolin-4-yl)-2-(2-oxopyrrolidin-1-yl)acetamide	NA	NA	NA	33,34
	Rolziracetam	2,6,7,8-tetrahydro-1H-pyrrolizine-3,5-dione	NA	~90	<25 min	35
	Dimiracetam	dihydro-1H-pyrrolo[1,2-a]imidazole-2,5(3H,6H)-diones	NA	NA	NA	36,37

a To compare the potencies for each drug, we calculated the daily treatment dose (assuming that the average weight of a patient is 60 kg) and defined the values as low (>50 mg/kg/d), medium (10–50 mg/kg/d) and high (<10 mg/kg/d).

b Selected pharmacokinetic outcome measures, bioavailability and half-life in plasma represent the values derived from pharmacokinetic examinations on humans, except those of aniracetam and rolziracetam, which were tested on rodents.

c Pharmacokinetic and dose values described in product insert as well as reference.

IUPAC = International Union of Pure and Applied Chemistry; **NA** = not available.

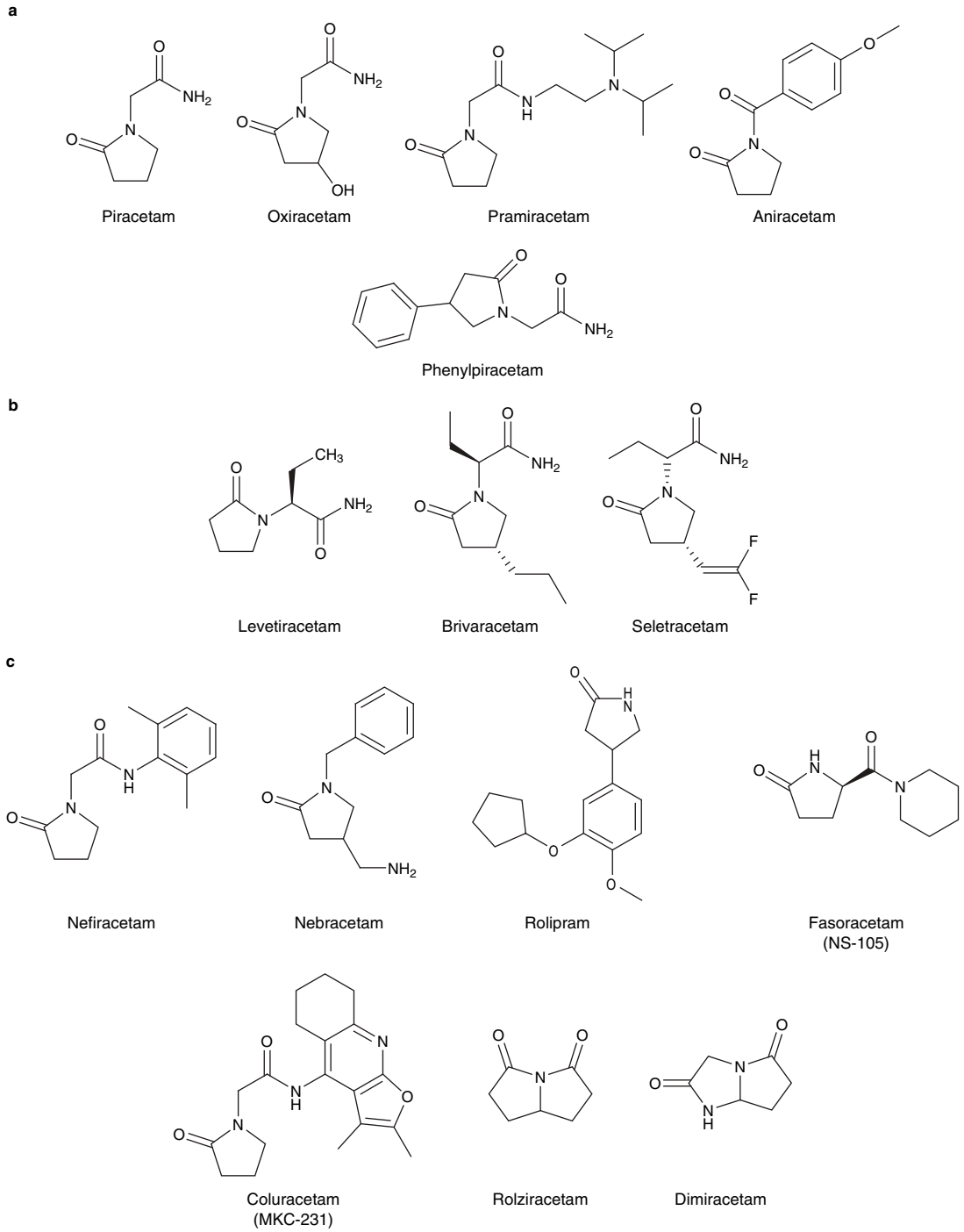

Fig. 1. Chemical structures and pharmacological properties of piracetam-like compounds: (**a**) subgroup 1 cognitive enhancers; (**b**) subgroup 2 antiepileptic drugs; and (**c**) subgroup 3 unknown clinical efficacy.

to subgroup 1 and/or their pharmacodynamic attributes. This contention applies particularly to subgroup 3 compounds, which indicate more extensive differences in their chemical structures than most other derivatives (table III, figure 1).

In contrast to subgroup 1 and 2 compounds, the subgroup 3 compound nefiracetam appears to potentiate NMDA receptors. In cultured cortical neurons of rats, this action occurs indirectly via activation of protein kinase C (PKC) and phosphorylation of one of the subunits of the heterotetramer NMDA receptor (NR1). This in turn enhances binding of glycine to NMDA, and removes the suppression of voltage-dependent currents caused by Mg^{2+} ions.[45] Expelling Mg^{2+} ions can open up the gate and allow Ca^{2+} to flow into the cytosol. This depolarization can cause a net positive and/or negative effect, as discussed previously. Furthermore, previous contradictory results regarding nefiracetam potentiation of $\alpha4\beta2$-type nACh receptors at various sites are possibly reconciled, considering that different PKC isozymes were involved in different tissues.[45]

On the other hand, nebracetam supposedly interacts largely with the ligand-gated NMDA receptor. This enables the drug to inhibit the (potentially lethal) excessive $[Ca^{2+}]i$ through NMDA channels, and to a lesser extent via the voltage-gated channels.[46,47] Fasoracetam modulates metabotropic glutamate receptor (mGluR) subclasses that are (positively and negatively) coupled to the G-protein receptor complex, thereby stimulating (or inhibiting) adenylate cyclase or cyclic adenosine monophosphate (cAMP) formation, which is implicated in a variety of signal transduction processes such as learning and memory. Its antagonist role was most evident in mitigating the deficits in learning and memory induced by one of the most potent $GABA_B$-mimetic drugs, baclofen, in rats.[48,49] Furthermore, repeat dose administration of fasoracetam upregulated $GABA_B$ receptors and that was linked to its promising antidepressant action in rats.[50] Coluracetam appears to function very differently, i.e. through trafficking of high-affinity choline transporters[51] and enhancing choline uptake in hippocampal synaptosomes, thus facilitating the synthesis, release and availability of acetylcholine.[52] The inter-relationships between these diverse complex processes would be challenging to dissect. These distinct and overlapping mechanisms may translate to additive, synergistic or antagonistic effects if more than one of these drugs is administered at a given time.

4. Pharmacology and Classification

For clarity in reviewing and analysing the data, we have separated the lead compounds into three subgroups. Subgroups 1 and 2 are based partly on the similarity of their molecular structures and partly on their therapeutic attributes. Subgroup 3 represents both old and new molecular entities with more diverse structures and unknown efficacies. Table III and figure 1 show this classification, as well as key pharmacokinetic properties for each compound. Major findings on pharmacological properties and stages of development for each subgroup are described in the following sections.

4.1 Subgroup 1: Cognitive Enhancers

4.1.1 Piracetam

Piracetam was first approved in Europe in the early 1970s for treatment of vertigo and age-related disorders. It is a non-potent drug (table III and figure 1); recent and ongoing trials have used escalating or various high doses depending upon the indication[6,53] (table IV). Adverse effects, although rare, mild and transitory, include anxiety, insomnia, drowsiness and agitation.[4,53]

Effect on Memory, Cognition, Attention, Depression

In the past decade, more than 20 review articles have been published showing the results of clinical trials and the use of piracetam in a variety of neurological disorders. A meta-analysis of 19 double-blind placebo-controlled trials performed between 1972 and 2001 on piracetam use in age-related mental impairments confirmed that individuals receiving piracetam improved by 60.9% compared with 32.5% in placebo, with a combined number needed to treat of 4.1, i.e. approximately four people had to receive piracetam to benefit one individual.[4] Since then, several

Table IV. Piracetam in clinical development[a]

Sponsor/study site	Intent to treat	Study design	No. of pts (age in y)	Dosage	Trial duration	Outcome measures	Efficacy summary (% improvement rate [APIR])	Adverse event	References
Piracetam									
Medical University, Berlin, Germany	Cognition/memory deficits after bypass surgery	rdbpc	120	Bolus 12 g preoperative infusion	3 d	Syndrome Kurztest and Alzheimer's disease assessment	46 ± 22	None	54
Humboldt University, Germany	Cognition/memory deficits after bypass surgery	rdbpc	64 (40–80, mean 63)	Bolus 12 g preoperative infusion	3 d	Short-term memory and attention tests	55 ± 20	None	55
University of Targu, Romania; University of Debrecen, Hungary	Cognition/memory deficits after bypass surgery	rdbpc	98 (44–65, mean 56)	↕ 12–24 g/d, IV then PO	6 wk	Psychological tests, cranial CT scans	29 ± 19	None	56
Russian State Medical University, Moscow, Russia	Cognition/memory in cerebrovascular disorders	Open-label, parallel	70 (45–75, mean 62)	(2) → 1.2 g/d, 2.4 g/d, PO	8 wk	MMSE Depression	13 ± 5 62 ± 20	Headache (15.7%)	57
Research Institute of Pharmacology, Moscow, Russia	Cognition/memory in cerebrovascular disorders and TBI	rac	53 (18–60)	(2) → 1.2 g/d, PO	56 d	MMSE CCSE	7 ± 3 8 ± 2	High blood pressure (18%)	58
Russian State Medical University, Moscow, Russia	Cognition/memory deficits (after TBI)	rpc	42 (12–18)	(3) → 1.2 g/d, 2.4 g/d, PO	1 mo	Memory and coordination tests	50 ± 11	None	59
UCB Pharma, Belgium	Mild cognitive impairment	rdbpc	675 (50–89, mean 68)	(3) → 4.8 g/d, 9.6 g/d, PO	12 mo	Cognitive scores, safety	None	None	60,61
McGill University, Montreal, QC, Canada	Myoclonus epilepsy	Open-label	11 (17–36, mean 24.5)	↑ 3.2–20 g/d, PO	18 mo	MII, seizure frequency	30 ± 13	Drowsiness	53

Continued next page

Table IV. Contd

Sponsor/study site	Intent to treat	Study design	No. of pts (age in y)	Dosage	Trial duration	Outcome measures	Efficacy summary (% improvement rate [APIR])	Adverse event	References
Beersheva Mental Health Center, Israel	Tardive dyskinesia	rdbpc crossover	40 (24–69, mean 47)	(2)→ 4.8 g/d	4 wk	Extrapyramidal symptom rating	38 ± 6	None	62,63
Marmara University, Turkey	Ataxia	Open-label	8 (mean 43.4)	↑ 30–60 g/d infusion	14 d	ICARS (such as posture and gait tests)	29 ± 19	None	64
Max-Plank-Institute, Dresden, Germany	Aphasia	rpc	24 (mean 57)	(2)→ 2 × 2.4 g/d, PO	6 wk	Language performance	20 ± 8	None	65
NIDA, Bethesda, MD, USA; University of Pennsylvania, PA, USA	Cocaine-related disorders	rdbpc	44	(2)→ 4.8 g/d, PO	10 wk	Anxiety, withdrawal symptoms	None	None	66-68
Piracetam + cinnarizine									
State Medical University, Moscow, Russia	CFS after encephalopathy (MS and TBI)	Open-label, parallel	29 MS 21 non-MS encephalopathies (20–57)	(2)→ 2.4 g/d, PO	1 mo	Depression, psychometric questionnaires	25 ± 8 15 ± 10	Sleep disturbance (12%)	69
Piracetam + risperidone									
Tehran University, Iran	Autism	rdbpc	40 (3–11)	↑ 200–800 mg/d, PO	10 wk	Psychometric ABC-C questionnaires	41 ± 11	Morning drowsiness	70

a The information summarized here was derived partly from the data submitted to the ClinicalTrials.gov databank (accessed 1 May 2009) and partly from articles entered in PubMed after the last meta-analysis in 2002.[4] To simplify presentations of the reported statistically significant data (test score numbers) for the efficacies, we calculated the total differences between test treatments and controls from baselines, and summarized as approximate percentage composite mean values or attributable percentage improvement rate.[71] 'None' denotes that there was no increase in the frequency or severity of adverse effects at the highest dose tested, which refers to the no observable adverse effect level dose.

ABC-C = Aberrant Behavior Checklist-Community; **APIR** = attributable percentage improvement rate (see Appendix); **CCSE** = cognitive capacity screening examination; **CFS** = chronic fatigue syndrome; **ICARS** = International Cooperative Ataxia Rating Scale; **IV** = intravenous injection; **MII** = Motor Impairment Index; **MMSE** = Mini Mental State Examination; **MS** = multiple sclerosis; **NIDA** = National Institute on Drug Abuse; **PO** = oral; **rac** = randomized, active controlled; **rdbpc** = randomized, double-blind, placebo-controlled; **rpc** = randomized, placebo-controlled; **TBI** = traumatic brain injury; ↑ indicates escalating dose; ↕ indicates escalating and de-escalating doses; **(2)→**, **(3)→** indicates parallel fixed doses.

new trials have been performed (table IV). Piracetam benefited most of the patients with cerebral ischaemia-induced short-term memory/cognitive deterioration after heart bypass surgery.[55] New data confirm a neuroprotective effect of piracetam for this intended use.[54] Consistent with this, an earlier study indicated that of numerous different tests related to visuomotor examinations, only the ability to recognize and shift numbers and letters (so-called 'trail-making') was considerably improved,[56] but the outcome was fairly variable (table IV). These independent cohort studies suggested that piracetam is neuroprotective.

It is noteworthy that, although piracetam treatment of patients with chronic cerebrovascular disorders showed only a modest improvement in memory, it considerably mitigated depression.[57] Such improvement rates in a wide range of age groups with diverse origins of cerebrovascular disorders were comparable.[58] However, in traumatic brain injury of adolescents the response rates to memory and attention were increased to approximately 60%[59] (table IV). These investigations suggest that piracetam is more effective in the latter cohorts.

Piracetam and its vasodilator partner drug cinnarizine (a calcium channel antagonist), as a combined product (Fezam®), modestly improved various cognitive abilities, such as activity/mood, in patients with multiple sclerosis (MS) with presumably 'ongoing' encephalopathies. However, it appears that it benefited non-MS patients with cerebral (post-traumatic) chronic lesions to a lesser extent. The most observed adverse event (AE) was a mild sleep disturbance[69] (table IV). Although the trial favoured MS patients, the subjectivity of (patient-reported) outcome measures complicates evaluations of these small cohort studies.

Based on the rationale that glutamatergic deficiency may be an underlying cause of autism, an investigational use of piracetam as add-on therapy to the antipsychotic risperidone in autistic children resulted in noticeably improved unusual behaviours, and was more effective than risperidone monotherapy, without apparently increasing AEs[70] (table IV). The positive trend began on week 2 and continued until the trial end on week 10, but the highest difference was only one standard deviation apart. A large trial would be useful to determine the extent of its long-term benefit. Piracetam use for several other expanded indications failed to demonstrate a beneficial effect, including older people with mild cognitive impairment (MCI) who were suspected of developing dementia,[60] electroconvulsive therapy-induced cognitive disturbances in schizophrenic patients or patients with depressive illness.[72] Moreover, it neither benefited cognitive functions in children with Down's syndrome[73] nor in abstinent people with cocaine addiction, although it surprisingly augmented cocaine-dependency[66] for reasons unknown.

Epilepsy, Convulsion, Seizure

Piracetam as add-on therapy to valproate or a combination of these with clonazepam significantly improved the motor impairment index in patients with myoclonus epilepsy[53] (table IV). In this structured protocol, an escalating dose was administered to the same treatment group, starting with a low dose with step increases every 4 days. This could arguably tolerise the patients to the drug uptake and/or turnover, hence compromising outcome measures. In tardive dyskinesia, which can occur as an adverse effect of conventional antipsychotic drugs such as chlorpromazine, approximately 67% of patients receiving piracetam responded favourably with a peak efficacy on week 4 compared with 24% on placebo (table IV); however, improved symptoms worsened after discontinuation of therapy.[62] The investigators stated that large well controlled trials are needed to determine the effectiveness of piracetam in this indication.

Neurodegenerative Disorders: Ataxia

Piracetam modestly benefited posture and gait disturbances, but not kinetic functions, speech and oculomotor disorders of patients with hereditary ataxia[64] (table IV). The drug was safe, but the study is too small to determine its real benefit-risk profile in ataxia. It also remains to be determined whether piracetam, or its derivative, would be effective in a non-hereditary ataxia.

Stroke/Ischaemia

A meta-analysis of studies in models of stroke/cerebral ischaemia in rats supports the potential effectiveness of piracetam.[5] The reviewers cautioned that the results were published at least 10 years after clinical trials and that the numbers of reliable studies are too small (six articles) to draw a robust conclusion, and reiterated that piracetam, but not oxiracetam and levetiracetam, decreased infarct volumes by almost 50%.[5] They also noted that these data are consistent with a *post hoc* clinical finding "if given soon after stroke onset, piracetam might have a beneficial effect" and "the failure of clinical trials with piracetam cannot therefore be taken as a failure animal modelling of stroke".[5] A previous Cochrane Review pointed out that piracetam is ineffective in patients with presumed ischaemic stroke, although other potential beneficial effects of piracetam remain unclear because of insufficient well controlled studies.[74] The strength of data derived from stroke modelling in rats and their relevance to humans are questionable. The negative outcome of clinical trials was based on survival rate assessment as the endpoint, not the infarct size as surrogate. Consistent with this, piracetam facilitated recovery of verbal skills in stroke patients with aphasia (confirmed by neuroimaging tests), but it failed to improve visuospatial and recognition memory, and cognitive functions such as reasoning[65] (table IV). Confirmatory results from large investigations are unavailable.

Vision

Piracetam also improved colour discrimination in patients (aged 19–24 years) who suffered from traumatic brain injuries of different severity. In this double-blind trial, patients were divided into three arms: (i) ten people with mild concussion; (ii) eight with minor concussion (both arms received piracetam); and (iii) four with mixed levels of concussion, who received placebo. Functional activity of the retina was evaluated by measurement of brightness sensitivity thresholds (BST) to four colours (blue, green, red and white; achromatic). BST scores significantly decreased in the test drug arms (blue 36% and 25%; green 20% and 17%; red 18% and 16%; and white 31% and 24%, respectively) but not in placebo, suggesting colour discrimination progress.[75] The investigators believed that piracetam improved retinal microcirculation and presumably acted as a GABA-mimetic drug, since GABA is also present in the retina. Using Fezam® for treatment of senile macular degeneration, the visual acuity improved significantly, though quite variably (50 ± 30%), in 76% of the eyes, and this was attributed to the vasoactive action of cinnarizine and the neurotonic effect of piracetam.[76]

4.1.2 Oxiracetam

With a hydroxyl group substitution in its oxopyrrolidone nucleus, oxiracetam exhibits a favourable pharmacokinetic profile and oral bioavailability[15] (table III, figure 1). It dose-dependently mitigated the scopolamine-induced deterioration of neuropsychological performance (e.g. semantic memory, word recall tests, reading) in a double-blind trial on 12 healthy volunteers.[77] Consistent with this, its use for 2–6 months in people aged >65 years improved certain of their cognitive deficits of nonspecific aetiology.[78] However, it failed to benefit patients with Alzheimer's disease (AD), although the length of treatment was only 1 month.[79] No AEs were noted.

4.1.3 Pramiracetam

Prepared by substitution of the amide of piracetam with the dipropan-2-ylaminoethyl group, pramiracetam exhibits a remarkable oral bioavailability and a variable half-life[16,17] (table III, figure 1). It is more potent and is thus used in lower doses than piracetam.[80] The only trial conducted in the US was in four young men who had cognitive problems after head injury and anoxia. It significantly improved some memory activities, especially delayed recall (30–50%) during 18 months of therapy and 1 month of follow-up.[81] However, there was a large variability in test results. Later, Italian researchers demonstrated the reduction of scopolamine-induced amnestic effects in healthy volunteers, i.e. two of five cognitive parameters (including tests for

immediate and delayed verbal recall) were approximately 50% better than those receiving placebo when tested 1 and 3 hours after scopolamine injection.[82] Two small trials were conducted in the Ukraine: one in patients with cerebrovascular disease[83] and another in patients with concussion.[84] The first trial claims that visual and verbal memories moderately improved in younger patients with chronic cerebrovascular and post-stroke cognitive symptoms, and to a lesser degree in older patients. The data in the second trial shows that pramiracetam was more effective than piracetam in restoring memory loss/disorientation in patients with mild craniocereberal traumas[84] (table V).

4.1.4 Aniracetam

An N-side chain modified derivative, aniracetam has low bioavailability in plasma and is eliminated rapidly in animals[102] (table III, figure 1). Considering issues in treating elderly people with renal dysfunction, its pharmacokinetics and the fate of metabolites were evaluated in six women (mean age 84.5 years) with cerebrovascular disease. The half-life of its major metabolites (anisic acid, *p*-methoxyhippuric acid, 2-pyrrolidone and succinimide) increased 4- to 7-fold compared with those in young healthy volunteers (0.79–1.58 hours). No adverse effects were noted.[18] It improved psychometric parameters up to 30% in aged MCI patients compared with placebo, with mild AEs apparently unrelated to aniracetam.[103] In another small trial involving elderly patients with slight to moderate vascular cerebral pathologies, it was reportedly useful.[104] However, aniracetam was not efficacious in people with memory/cognitive impairments associated with chronic exposure to hazardous organic solvents.[105]

4.1.5 Phenylpiracetam

A phenyl derivative of piracetam, phenotropil or phenotropyl is absorbed fast and exhibits high oral bioavailability (Phenotropil®, product insert). Studies on rodents (100 mg/kg, intramuscular, oral) showed absorption time of <1 hour and half-life of 2.5–3 hours,[19,20] but its pharmacokinetic profiles in humans are unpublished. It demonstrates multitherapeutic potential, some in common with subgroup 2 AEDs.

Memory, Cognition, Attention, Depression

Phenylpiracetam is reportedly beneficial to people who develop cognitive deficits and/or depression after encephalopathy and brain injures (table V). It increased quality of life in patients with encephalopathy after acute lesions (30 people), brain traumas (33 people) and gliomas surgery (36 people). The average minimental state examination (MMSE) scores (a standard 30-point questionnaire used to assess cognition) from baseline improved in all groups. In the end, anxiety improved and depression declined substantially, and that resulted in less discomfort and better ability to execute everyday activities.[85] Recovery of memory, attention and sensomotor disturbances were indistinguishable for similar treatments in mild cranial brain traumas. The differences noted favoured phenylpiracetam over piracetam because of faster alleviation of headaches and a general fatigue after 7 and 14 days.[86] Phenylpiracetam was favoured in the treatment of chronic vascular encephalopathy as it improved the cognitive performance in all tests, whereas only two of the eight test scores increased in the piracetam arm.[87] It also improved both asthenia and depression scores, albeit to a lesser extent in MS patients.[88]

In a comparative trial, asthenia and chronic fatigue syndrome (CFS) patients were treated with phenylpiracetam (68 people), piracetam (65 people) and placebo (47 people). The scores of the ten-word memory test and attention switching tests for the phenylpiracetam improved relative to those of piracetam and placebo. Overall, 83% of asthenic and 87% of CFS patients responded well to phenylpiracetam versus 48% and 55%, respectively, to piracetam.[89] In agreement with this, phenylpiracetam markedly increased the problem-solving skills of adolescents with asthenia who were A-players, B-players and C-players (i.e. the number of individuals able to respond to the memory and attention tests after the first, second and third attempts) from 11%, 15%, 73% before to 23%, 40%, 37% after treatment, respectively. It was superior to piracetam

Table V. Piracetam-like compounds in clinical development

Sponsor/study site	Intent to treat	Study design	No. of pts (age in y)	Dosage (mg/d, oral)	Trial duration	Outcome measures	Efficacy summary (% improvement rate)	Adverse event	References
Pramiracetam									
Army Central Hospital, Kiev, Ukraine	Cognition/memory deficits (after TBI)	Active (piracetam) controlled	65 (16–60, mean 31)	(2)→ 600	1 mo	Amnesia and orientation	Tx 86 Cx 60	NA	84
Phenylpiracetam									
Omsk State Medical Academy, Russia	Encephalopathy (gliomas to acute lesions)	Open-label	99 (40–60)	200	1 mo	MMSE Anxiety Depression	Tx 45 ± 16 50 ± 5 38 ± 4	None	85
Navy Hospital, Vladivostok, Russia	Encephalopathy (after TBI)	Active controlled	56 (20–30)	(2)→ 100	1 mo	Asthenia, headache	ND	None	86
Nizhny Novgorod State Medical Academy, Russia	Encephalopathy (vascular)	Active controlled	51 (mean 57.2)	(2)→ 200	1 mo	Neurological and psychological	Tx 32 ± 11 Cx 25 ± 11	None	87
Multiple Sclerosis Center of Novosibirsk, Russia	Multiple sclerosis	Open-label	39	200	1 mo	Asthenia Anxiety Depression	11 20 21	Sleep disturbance	88
National Research Center for Social and Forensic Psychiatry, Moscow, Russia	Asthenia/fatigue syndrome	Active and placebo controlled	180 (21–40, mean 25	(3)→ 100–200	1 mo	Memory (10-word test)	Tx 88 ± 52 Cx 37 ± 19 PL 16 ± 13	None	89
Clinic No. 28, Volgograd, Russia	Asthenia	Active controlled	39 (14–19, mean 15)	(2)→ 100	1 mo	Problem solving	ND	None	90
Ural State Medical Academy, Chelyabinsk, Russia	Epilepsy	rpc	61 (mean 29.7)	(2)→ 100	2 mo	Seizure: Total no. Frequency	Tx 46 ± 1 46 ± 3	None	91

Continued next page

Table V. Contd

Sponsor/study site	Intent to treat	Study design	No. of pts (age in y)	Dosage (mg/d, oral)	Trial duration	Outcome measures	Efficacy summary (% improvement rate)	Adverse event	References
Gorbunov Hospital, Kemerovo, Russia	Epilepsy	rpc	40 (17–20)	(2)→ 100	1 mo	MMSE	12	None	92
Tver State Medical Academy, Russia	Cerebral stroke	Open-label	20 (31–67, mean 52)	100	1 mo	Ab titres: MMP PHL	Tx 34 ± 4 7.5 ± 0.6	None	93
Regional Neurologic Department, Moscow, Russia	Cerebral stroke (ischaemic)	Open-label	120	(3)→ 100, 200	1 mo	MMSE Barthel index Stroke scale	Tx 10 ± 0.4 6 ± 0.4 9.1	Nausea (3%)	94
Orel State University, Russia	Glaucoma	Open-label	26	100	1 mo	Vision acuity	Tx 16 ± 8	None	95
Nefiracetam									
Daiichi Sankyo, Tokyo, Japan; Prestwick Clinical, Washington, DC, USA	Poststroke depression	rdbpc	159 (mean 66.8)	(3)→ 600, 900	12 wk	Depression Apathy	None Tx 34 PL 5	None	96 97
NINDS	Alzheimer's disease	Open-label	50 (50–90)	NA	20 wk	NA	NA	NA	98
Rolipram									
NIMH	Major depressive disorder	rdbpc	50 (18–65)	NA	3 y	Depression, PDE4 test	NA	NA	99
NINDS	Multiple sclerosis	Open-label	6 (18–65)	7.5–9	8 mo	MRI	None	Poor tolerability	100,101

Ab = antibody; **Cx** = control; **MMP** = main myelin protein; **MMSE** = Mini Mental State Examination; **MRI** = magnetic resonance imaging; **NA** = not available; **ND** = not done (test scores lacking); **NINDS** = National Institute of Neurological Disorders and Stroke; **NIMH** = National Institute of Mental Health; **PDE4** = phosphodiesterase type 4; **PHL** = phospholipids; **PL** = placebo; **rdbpc** = randomized, double-blind, placebo-controlled; **rpc** = randomized, placebo controlled; **TBI** = traumatic brain injury; **Tx** = test agent; **(2)→**, **(3)→** indicates parallel fixed doses.

(400 mg/day) in combination with multivitamins and physiotherapy.[90] It is unclear whether any particular patient(s) was unresponsive to or relapsed after therapy.

Convulsion/Epilepsy, Seizure

Phenylpiracetam exhibited an antiepileptic action in rodents. Its effective dose (300 mg/kg) decreased the metrazol (a drug used as a circulatory and respiratory stimulant)-induced seizure by 50%.[106] Phenylpiracetam was administered to patients in addition to one standard AED (including valproyl amide, carbamazepine, lamotrigine, topiramate or a barbiturate, or structured polytherapy with more than one of these drugs). It substantially mitigated the number and frequency of seizures of patients receiving AED only and the number of individuals with a desynchronous EEG profile decreased from eight to three, while the number of individuals with seizure remissions increased modestly.[91] Consistent with this, cognitive functions in epileptic patients based on an MMSE test improved to only a small extent.[92] These trials favoured phenylpiracetam as add-on medication for epilepsy (table V).

Cerebral Stroke/Ischaemia

Because the immune system has a crucial role in the pathogenesis of ischaemia-stroke, titres of antibodies against the main myelin protein and phospholipids were measured in patients with acute cerebral stroke treated with phenylpiracetam. The titres of both antibodies decreased, suggesting possible reduction of ongoing demyelination[93] (table V). In a two-arm parallel trial with patients receiving one tablet (80 people) and two tablets (40 people) a day, both MMSE and severity of stroke scores improved significantly, while only showing a trend toward improvement in daily living activities (Barthel test).[94] A *post hoc* analysis for a subset of these data might be useful, but overall the therapy appears modestly beneficial (table V).

Vision/Glaucoma

The cause of blindness in glaucoma is optical neuropathy and ganglia cell apoptosis. Use of a neuroprotective agent in delaying or preventing ganglial cell death was the rationale of a recent trial. Phenylpiracetam was given to patients with unstable open-angle glaucomas after the eye pressures were normalized using ocular hypotensive therapy and laser trabeculoplasty. The average number of blind spots or islands of loss or impairment of visual acuity decreased, and glaucoma stabilized in 80% of patients at 6-month follow-up[95] (table V). It is premature to conclude whether the trial favours phenylpiracetam because of the lack of a prospective placebo control and possible variables such as patient heterogeneity at the trial entry point.

4.2 Subgroup 2: Antiepileptic/Anticonvulsive Drugs

This subgroup is discussed briefly in the following sections because of their approved and purported activities as AEDs. These drugs have been reviewed recently by others (e.g. Bialer et al.,[107] Rogawski[108] and Pollard[109]) and will be topics of reviews in the future.

4.2.1 Levetiracetam

Levetiracetam is a second-generation homologue of piracetam with an α-ethyl side-chain substitution that has a favourable pharmacokinetic and safety profile,[110] and is the only approved drug in this subgroup (table III, figure 1). Other recent reviews have called into question the safety of levetiracetam because of its potential adverse effects on bone strength and formation,[111] as well as behaviour or mood.[112] However, it improved memory and cognitive functions in patients with refractory partial seizures[113] and language dysfunctions in children with benign sporadic seizures,[114] in a small controlled trial and an open-label study, respectively. A retrospective analysis[115] and non-controlled trials in both non-epileptic[116] and epileptic[117] patients with anxiety and/or depression suggested that levetiracetam is effective to some extent. These results could suggest that levetiracetam is a pluripotent compound, which means it is stimulatory to certain behaviours and inhibitory to other functions. However, its beneficial effect (as a monotherapy) for other indications such as autism is controversial. In

constrast to a previous report, it did not inhibit behavioural disturbances in autistic children.[118] As a monotherapy, it was ineffective for treatment of corticosteroid-induced mood and cognitive impairment.[119] Whether levetiracetam would work better than piracetam if given as a complementary medication, similar to the piracetam with risperidone protocol,[66] is unknown.

4.2.2 Brivaracetam and Seletracetam

The 4-n-propyl homologue brivaracetam and the difluoroethenyled derivative seletracetam (next-generation drugs to levetiracetam) have more recently been attributed with potentially superior antiepileptic activities based on *in vitro* drug screening and animal tests.[42,43,107] The higher potency and apparently common mechanisms of action demonstrated for both brivaracetam and seletracetam are partially consistent with clinical results. Both exhibited promising, although less than anticipated benefits in phase II trials.[108,120]

Brivaracetam was safe in healthy volunteers. It is readily absorbed after oral administration, reaching maximum plasma concentration in 0.5–1 hours, and eliminated with a half-life of 7–8 hours. The most common AEs (mild to moderate) were somnolence and dizziness (similar to levetiracetam), especially at high doses.[21,22] It produced a reduction of seizure frequencies in 55% of patients and the elimination of seizure in about 8%.[120] Brivaracetam as adjunctive therapy was well tolerated in refractory partial-onset seizures in adults according to a presentation at the 2007 Epilepsy Conference,[121] although it failed to decrease the frequency of seizures during 7 weeks' treatment.[122] Although both drugs may be non-inferior if not superior to levetiracetam, it seems that there is a level of uncertainty in continuing some trials; development of brivaracetam for epilepsy, Unverricht-Landborg disease and nerve pain appears to be in progress, but seletracetam development seems to be on hold.[109]

4.3 Subgroup 3: Compounds with Unknown Efficacy

4.3.1 Nefiracetam

Nefiracetam is being developed for the treatment of dementia (AD and vascular type). It potentiated nicotinic acetylcholine receptors in rat cortical neuronal primary culture at very low concentrations (0.1–1 nmol/L); thus, it is highly potent.[25,123] In humans, its concentration in blood peaked in 2 hours with half-life of 3–5 hours[26] (table III, figure 1). A phase II trial of nefiracetam for AD patients is completed, but the results are unpublished. In addition, nefiracetam failed to demonstrate efficacy in a 12-week trial on cognitive deficits in patients with major depression after stroke.[96] Subsequent analysis showed noticeably improved apathy in a subpopulation of the same individuals (table V).[97] Whether this drug in combination with other agents will be more effective for these or other indications is unexplored.

4.3.2 Nebracetam

Nebracetam (WEB 1881 FU) is a cholinergic agent that has been predominantly studied in Japan since the late 1980s. In animals it was neuroprotective, possibly via enhancing both cholinergic and limbic noradrenergic functions of the hippocampus.[27] Histological evidence indicated that it is protective against ischaemic delayed neuronal cell death in the hippocampus of stroke-prone rats.[28] Clinical trials in healthy volunteers in Germany were conducted to determine whether it affected event-related cerebral potentials[124] and visual spatial attention.[125] Both investigations revealed no significant effects on memory performance. Nonetheless, a small trial in nine AD patients demonstrated a promising improvement of dementia.[126]

4.3.3 Rolipram

The analogue rolipram, distantly related to piracetam, inhibits phosphodiesterase type 4 (PDE4). It has a good bioavailability and short half-life[29] (table III, figure 1), and was apparently safe within the dose range of 0.75–3 mg/day in humans.[30] It was tested as an antidepressant in several clinical trials, but it was not better than available drugs such as amitriptyline[127,128] and imipramine.[129,130] Its typical adverse effect was nausea, which presumably compromised its use as an antidepressant. The neuroprotective effect of rolipram was evident in cultured cells and in

animals. Interestingly, it promoted regeneration of axons[131] and induced phrenic nerve recovery after cervical spinal cord injury in rats.[132] These findings support its potential use for similar conditions in humans. However, rolipram failed to suppress inflammation in the brain of MS patients and even showed increased inflammatory activity (table V).[100,101] Recently, another clinical trial began to investigate the correlation between depression and modulation of cAMP-specific PDE4 levels (table V). Additional investigation of the potential clinical use of rolipram appears underway, which involves treatment of memory and learning deficits after microsphere embolism-induced cerebral ischaemia.[133]

4.3.4 Fasoracetam

Fasoracetam (NS 105, LAM 105) is a relatively new candidate drug, which has potential as a cognitive enhancer. It is absorbed rapidly after oral administration in rats (maximum concentration reached after 0.5 hours), distributes intact[134] and excretes predominantly unchanged from kidneys.[31] Bioavailability in rats, dogs and monkeys were 97%, 90% and 79%, with a half-life of 0.91, 2.8 and 1.3 hours, respectively.[31] It takes a little longer for this drug to clear in elderly people (half-life = 5.17 hours) than in young people (4.45 hours),[32] which might limit its utility, especially if it causes prolonged adverse drug interactions. Its safety and efficacy have not been determined yet.

4.3.5 Coluracetam

Coluracetam (MKC-231) is a quinolin derivative of piracetam and a choline-uptake enhancer that is being explored in Japan. This distinctly novel compound improved an artificially induced memory impairment loss in rats.[33] A daily repeat dosing study showed a long-lasting effect in rodents.[34] Data related to its pharmacokinetic and pharmatoxicological properties are unpublished.

4.3.6 Rolziracetam

Rolziracetam is a cyclic imide that improved performance of a delayed-response task in aged Rhesus monkeys.[71] As a result, this drug was proposed as a good candidate for the treatment of cognitive impairment in humans. However, it was shown later that it is quite unstable *in vivo* (half-life <25 minutes) and is eliminated in a metabolized form as 5-oxo-2-pyrrolodinepropanoic acid via urinary excretion in rats.[35] This has possibly slowed down its development.

4.3.7 Dimiracetam

A series of bicyclic pyrrolidinone analogues of piracetam have been synthesized and tested for their ability to reverse scopolamine-induced amnesia in rodents.[36] One such compound is dimiracetam, which was 10- to 30-fold more potent than oxiracetam. Dimiracetam congeners reportedly had beneficial effects on peripheral neuropathic pain in rats.[37] With respect to its effect site, the activities and bioavailability of these compounds in the brain are unknown. The causes of peripheral neuropathic pain are generally associated with damage to the peripheral tissues outside of the CNS. There is no evidence to suggest that piracetam, or its derivatives, are effective analgesic medications.

5. Discussion

Subgroup 1 and 2 compounds are the most researched among nootropic drugs, some with proven efficacy and some with unsubstantiated claims. The piracetam-like compounds with chemical structures most closely related to piracetam, including the oxopyrrolidone ring and its alkylamine branch, resemble certain amino acids (such as glycine, proline or hydroxyproline, and glutamate, which also act as neurotransmitters). The oxopyrrolidone ring is generally recognized as safe because its polymeric cross-linked form, polyvinylpyrrolidone, is used as a disintegrant and coating excipient in tablet manufacture. Some piracetam-like compounds indeed exhibit similar modes of action as well as overlapping pharmacokinetic profiles. These features, in part, can explain the observed high degree of safety for piracetam compounds.

In contrast, the molecular entities in subgroup 3 can possibly exhibit other undesirable side effects, e.g. the overinduction of certain first-pass metabolic enzymes or undesirable interaction with non-target sites. Thus, it is important to

investigate their mechanisms of action as well as their other biochemical properties. Potential drug-to-drug interactions in combination therapies are important, albeit that little research has been done with lead drugs of the piracetam family. It appears that there is no general corollary of evidence between drugs potencies, bioavailabilities, pharmacokinetics, and their safety and efficacy.

The relevance of the mechanisms of action of these drugs to the known deficiencies of both glutamate receptors, such as NMDA, and nACh receptors in the brain of AD patients are important, and research in this area will continue to unfold new insights. At least some of the subgroup 3 drugs may be useful for the treatment of various cognitive dysfunctions and/or AD patients. However, overstimulation of, for instance, NMDA receptors could cause toxicity and cell death. The molecular structures of subgroup 1 and 2 compounds differ only very slightly. It seems perplexing that the mechanisms modulating Ca^{2+} currents for the subgroup 1 compounds (piracetam, oxiracetam, aniracetam) are distinctly different from those of subgroup 2 (particularly levetiracetam), which results in the opposite direction and flow of Ca^{2+} currents in neurons. Although neuromodulatory substances can be agonists or antagonists, such conflicting functions are generally dose dependent.

Inadequate data exist on how these compounds, including active agents outside this family of nootrops, impact on brain performance when given as a combined drug product. To improve the efficacy of piracetam-like drugs, future research will probably focus on designing newer small molecule compounds to enable a higher potency, better target bioavailability and tolerability, and thus be suitable for longer-term use. Researchers in this area are also likely to focus on the novel prodrugs of piracetam that can enable sustained delivery and higher permeability, especially across the blood-brain barrier. To achieve this, it may be necessary to generate rationally designed drugs for a set of prespecified target receptors. Alternatively, novel derivatives may be designed with a dual property to affect receptors in CNS and peripheral neurons.

Numerous reports have recently reiterated that the glutamate receptors are associated with broad important functions of the brain, including memory and learning,[135] anxiety and depression.[136] These receptors are also connected to pain,[137] and neurodegenerative[138] as well as neuronal cell repair processes.[139] Notably, the activation of ionotropic glutamate receptors increases $[Ca^{2+}]i$, which, if it exceeds normal physiological concentrations in neurons, can in turn cause toxic injury and neuronal cell death.[140] An overstimulation and release of glutamate lets in calcium and increases its intracellular deposit, a key step that triggers (glutamate-/$[Ca^{2+}]i$-induced) neurotoxicity in both hippocampal and cerebral Purkinje neurons[141,142] (reviewed by Mattson[143]). The excess calcium influx activates destructive cysteine proteases, such as calpains, through a variety of biochemical processes, which leads to proteolysis of glutamate receptor proteins, including AMPA[141,142] and NMDA.[144] The ensuing calcification, among other factors, can then cause neuronal apoptosis or degeneration of 'dark cells', and lead to deleterious side effects. These actions would raise a safety concern for the compounds disturbing the homeostasis of ionotropic glutamate receptors. Whether or not the subgroup 1 drugs pose a long-term risk based on this possibility has not been thoroughly explored.

It would be desirable if a piracetam-like ligand polarizes the glutamate receptor to an extent that it reverses the current and decreases calcium overload in neurons. This can have a beneficial (neuroprotective) effect, resulting in inhibition of $[Ca^{2+}]i$-mediated neuronal cell death. Consistent with this, deactivation of AMPA receptors in cultured neurons of the hippocampus and cerebellum decreases intracellular calcium load and this leads to neuroprotection.[141,142] The key significance of the latter model is that some of the crucial roles of the hippocampus have been implicated in spatial learning (the ability to remember to find the way to a given place), 'construction of mental images' and long-term memories.[145,146] Importantly, piracetam-like drugs can affect different parts of brain tissue, from the cortical motor region to deep neurons in the

hippocampus. This region of the brain is compromised in aging people and deteriorates especially in CNS disorders such as AD.[147] As the role of calcium in neuronal growth and plasticity is beginning to unfold, a positive regulation of homeostasis that prevents disturbances in cellular Ca^{2+} can be neuroprotective in people with MCI and AD.[138,143] However, the previous reports come short of validating the mechanisms of action of piracetam nootrops before their clinical efficacies were established. Glutamate receptors also serve as biological targets for non-piracetam-like nootropic drugs such as acetyl-L-carnitine, which reportedly increased expression of mGluR (type 2 protein) in the cerebral cortex as well as spinal cord of rats, though not in the cerebellum or hippocampus.[148] In addition, acetyl-L-carnitine protected hippocampus from hypoxia-induced neuronal damage and improved spatial memory deficits in rats, by reversing the aberrant expression of the NR1 subunit of the NMDA receptor and apoptotic proteins.[149] Notably, its unacetylated form, L-carnitine, protected rat pups from the neurotoxic adverse effects of isoflurane and nitrous oxide. These anaesthetic gases, which are used in surgical procedures for human infants and in animals, block NMDA or potentiate GABA receptors.[150] Although the neuroprotective effect of L-carnitine is probably through removal of toxic fatty acid accumulations in neurons, acetyl-L-carnitine may also affect neurotransmitter receptors.

It will be of interest to determine whether non-piracetam nootrops such as acetyl-L-carnitine can synergize with a piracetam-like compound. We draw this hypothesis from independent published papers showing that acetyl-L-carnitine increases expression of type 2 metabotropic glutamate receptors in neurons (a mechanism consistent with abilities of acetyl-L-carnitine to increase nerve conduction velocity, decrease neuronal loss and promote nerve regeneration)[148] and that some piracetam compounds interact with glutamate receptors. In moderate to severe AD both glutamate and cholinergic receptors are downregulated.[151] These compounds were investigated for their ability to improve memory in AD, and have been implicated to be neuroprotective in an aging brain model in rats. Whether a combination of acetyl-L-carnitine and a piracetam-like active would exhibit a synergetic effect remains to be determined.

Meta-analysis in and out of itself carries a probability of error. Failure to consider the confounding variables for outcome measures, especially in a large data pool (in addition to factors such as sample heterogeneity across and within studies and potential publication biases), can lead to overstatements of efficacy or positive predicative value while potentially underestimating negative predictive value and adverse effects. This is consistent with the concerns of the authors of a recent review and meta-analysis of piracetam and piracetam-like drugs in stroke models in rodents,[5] e.g. inclusion of a selected few articles could disproportionately favour the efficacy findings. Interestingly, efficacy of piracetam was the highest when halothane anaesthesia was used.[5] In this context, piracetam was neuroprotective against lesion induction, but it was given as an acute treatment. We offer a different explanation, which is that piracetam possibly acted as an antagonist to halothane, hence attenuating the neurotoxic adverse effect of this general anaesthetic (which has recently been abandoned for human use), and that could be the underlying mechanism of piracetam in reducing cerebral infarctions in rats. Finally, potential interactions of piracetam-like drugs with the actions of other drugs in polytherapies are the subject of a separate review.

Overall, the published data predominantly state that lead drugs in clinical use are generally safe and effective, although most outcome measures appear inconclusive and/or too premature to draw a definitive conclusion. The compounds that demonstrate no observable adverse effect level (NOAEL) at high doses were mostly explored for broad indications. While several expanded trials revealed few beneficial effects, such investigations are likely to continue for multiple reasons. Chief among them, an auxiliary drug can complement suboptimal drugs, and this would be cost effective. A development strategy relying solely on old drugs simply because of their favourable benefit-risk profile can also be

counterproductive, potentially detracting from the creation of innovative new drugs. Future research has to reconcile the remaining issues and come up with more rational designs or better alternatives.

6. Conclusion

The current trend of research is gearing more towards testing piracetam and piracetam-like compounds for new indications. Many trials started with insufficient prior explorations in animal models of human diseases. The efficacies of these drugs for most indications appear promising, although most trials are inconclusive and well controlled studies are required. Their potential neuroprotective and neuroregenerative effects are the least explored. The low to moderate potencies of most of these active agents and their lack of target specificities may have contributed to some of their suboptimal efficacy. Unlike most GABA-mimetic drugs (such as barbiturates, carbamazepines and gabazine [SR-95531]) that can cause the AE of amnesia, piracetam and some piracetam-like drugs are relatively safe, and are dynamic and flexible enough to develop for different indications. Long-term consequences and potential risks associated with off-label use of these drugs are unidentified. Their mechanisms of action have also been inadequately researched. Potential biases in the design, disease modelling and interpretation of outcome measures for expanded trials are difficult to rule out, especially after the effectiveness of a given drug is revealed. Improvements to the design of newer-generation chemical entities can lead to better clinical efficacy.

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Appendix

Explanation of attributable percentage improvement rate (APIR) calculations.

The test scores in various clinical trials represent a set of incomparable numerical values, and the statistical inferences of such data indicate little or nothing of the size of potential difference or clinical importance. For clarity, uniformity and comparability we used the following formulas:

$$\mathrm{APIR}\% = \frac{(\mathrm{Bp} - \mathrm{p}) - (\mathrm{Bt} - \mathrm{Tx})}{(\mathrm{Bp} - \mathrm{p})} \times 100$$

or

$$\mathrm{APIR}\% = \frac{(\mathrm{Bt} - \mathrm{Tx})}{\mathrm{Bt}} \times 100$$

where Bp and Bt are placebo and test agent baselines, respectively, P is placebo and Tx is the test agent, to estimate the percentage improvement rates. The APIRs, or the composite mean values, were calculated for the outcome measures that were significant ($p \leq 0.05$).

For example, in the study by Holinski et al.[54] (table IV), score values decreased in both test and placebo arms, compared with baseline. The effect of the test agent resulted in lesser decline. The overall cognitive function score at baseline was 0.06 ± 1.02 and -0.06 ± 0.99 in the test and placebo arms. The outcome measure values were -0.65 ± 0.93 and -1.38 ± 1.1, correspondingly.

$$\mathrm{APIR}\% = \frac{[(-0.06) - (-1.38)] - [(-0.06) - (0.65)]}{(-0.06) - (-1.38)} \times 100 = 46\%$$

For trials, where the outcomes were compared with baselines, we used the second formula as follows:

$$\mathrm{APIR}\% = \frac{34.6 - 29.5}{34.6} \times 100 = 15\%$$

In the study by Batysheva et al.,[57] for example, the activity test score was 34.6 ± 1.34 at baseline and 29.5 ± 1.43 after the treatment.

Percentage standard deviations (± SD%) were calculated based on three values: APIR 'low', APIR 'mean' and APIR 'high'. Lower limit value = test score mean value − SD; upper limit value = test score mean value + SD.

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Correspondence: Dr *M. Reza Sadaie*, NovoMed Consulting, 12214 Plum Orchard Drive, Silver Spring, MD 20904, USA. E-mail: rsadaie@novomedconsulting.com