**Review**

# Medical aspects of learning disorders: role of nootropic drugs

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**Abstract**

Learning disabilities are a spectrum of disorders affecting people who have no sensory or mental deficiency by definition. Dyslexia is the most common learning disability among those diagnosed with the disorder. Three theories have been advanced to explain dyslexia—phonological, cerebellar, and magnocellular theories. Genetic studies identified loci on chromosomes 6 and 15, and linkage studies found sites on 1, 2, 3, 7, and 18. Remediation of learning disabled (LD) children has been and still is the only available method to intervene and help such children. Nootropic drugs, the prototype of which is Piracetam, have been in clinical practice in France since 1970. They have proven efficacy in animal and human studies concerning learning. A review of the available documentation of those studies is provided, leading to the conclusion that nootropic drugs may benefit those children as part of a multimodal approach to manage learning disabilities.


*Keywords:* learning disabilities, dyslexia, dysgraphia, dyscalculia

## 1. Introduction

Learning disabilities is a term referring to a heterogeneous group of neurobehavioral disorders manifested by significant unexpected specific and persistent difficulties in the acquisition and use of efficient reading (dyslexia), writing (dysgraphia) or mathematical (dyscalculia) abilities, despite conventional instruction, intact senses, normal intelligence, proper motivation and adequate socio-cultural opportunity [1-4].

W. Pringle Morgan of Sussex, England published the first description of the learning disorder that would come to be known as developmental dyslexia in the 1896 *British Medical Journal*: "Percy F., aged 14, has always been a bright and intelligent boy, quick at games, and in no way inferior to others of his age. His great difficulty has been—and is now—his inability to learn to read [5]."

The Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV), published by the American Psychiatric Association in 1994, reports prevalence estimates of 2-10% for Learning Disorders (LDs), depending on the nature of ascertainment and the definitions applied. While up to 3% of children in France present severe and specific language and/or reading disorders [6], in the United Kingdom, estimates of prevalence vary, according to a parliamentary report, from 2 to 15% of the population [7].

It is estimated that about 5 to 10% of school-aged population in the United States have been identified with learning disabilities and that up to 5% of all office visits to a pediatrician and up to 50% of children evaluated in mental health clinics have learning disabilities [8]. Dyslexia is the most common type of learning disability, affecting 80% of children diagnosed as learning disabled [2].

## 2. Etiology

Evidences for the origin of dyslexia have been increasingly accumulating. Although multiple etiologies are proposed for this complex trait, the exact cause still remains unknown; but substantial evidence from genetic and neurological studies suggest that dyslexia is a disorder influenced by genetic factors with the underlying deficit being in the language areas of the brain [9].

Recent functional MRI (fMRI) brain studies indicate that the disorder may be caused by specific deficits in the left fronto temporal region or atypical asymmetries in the left perisylvian regions [10].

## 3. Genetics

It has been known for decades that learning disorders run in families. In the 1990s, family aggregation studies, twin studies, and genetic linkage analyses confirmed the strong hereditary influences on reading and mathematics disorders. Genetic studies also confirm the heterogeneity of the phenotype [11].

In monozygotic twins, different measures of dyslexia, phonological awareness and phonological coding, are highly heritable (50 to 70%) and more frequent than dizygotic twins [12].

As reading is a complex task, this disability could arise from deficiencies in one or more associated cognitive processes. Because of the complex nature of the problem, identification of dyslexia genes is a difficult task most likely to be influenced by the interaction of multiple genetic and environmental factors [13].

The causes of the malformations in the dyslexic brain remained unclear until four candidate dyslexia susceptibility genes on chromosome 6 were reported—DYX1C1, KIAA0319, DCDC2 and ROBO1—which are involved in neuronal migra-

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tion and other developmental processes. Experimental interference with these genes leads to neuronal migration anomalies [14].

Evidence has accumulated that location on the short arm of chromosome 6 (6p21.3), the short arm of chromosome 15, and loci on chromosomes 1, 2, 3, 7 and 18 are related to dyslexia (see listing of studies in [9,11]). Genetic linkage studies have implicated loci on chromosomes 6 and 15 in dyslexia [15].

## 4. Theories

There are three main theories that have been advanced to explain the etiology of dyslexia.

### 4.1 The phonological theory of dyslexia

Brain recognizes language in a hierarchical order. The upper levels deal with semantics (the meaning of words), syntax (grammatical structure) and discourse (connected sentences). The lower levels of hierarchy deal with breaking sounds into separate small units called phonemes. Thus before words can be comprehended at higher levels in the hierarchy, they have to be decomposed into phonologic constituents that the alphabetic characters represent. To achieve this, the reader should have conscious awareness of the phonological structure of spoken words. If the reader lacks this awareness, he will have difficulty in learning the relationship between letters and sounds, as well as applying those letter/sound correspondences to sound out unknown words [16].

Individuals with dyslexia have difficulties with phonological decoding of orthographic symbols, and this is the significant source of reading problems [17].

Since most dyslexics show deficits in phoneme processing, it was suggested that phonological deficit is the most significant and consistent marker of dyslexia [18].

Brain imaging studies in dyslexics, in response to a phonological task, indicate under-activation of posterior brain regions (Wernickes's area, angular gyrus, extrastriate and striate cortex) and relative over-activation in anterior regions (inferior frontal gyrus). These brain activation patterns provide evidence of an imperfectly functioning brain system for segmenting words into their phonologic constituents [19,20].

### 4.2 The cerebellar theory of dyslexia

This theory postulates that the cerebellum of dyslexics is somewhat dysfunctional. In support of this theory are the frequently associated lack of coordination, balance and time estimation [20].

The normal pattern of cerebellar asymmetry is anomalous in dyslexia. The ratio of left grey matter was greater in the cerebella of those with dyslexia than in the controls. Those with more symmetric cerebella made more errors on a nonsense word reading measure of phonological decoding deficit [21]. The right cerebellum was also shown to display a functional deficit in dyslexics—exhibiting decreased blood flow in response to both learned and novel motor tasks [22].

There is evidence of reduced cerebellar activity in dyslexics performing motor learning tasks. This is evident in delayed motor milestones such as crawling, walking, and a characteristic clumsiness [23].

### 4.3 The magnocellular theory of dyslexia

Neurons in the magnocellular layers of the lateral geniculate nucleus are sensitive to motion perception and temporal resolution and are important for the control of eye movements [24].

Impaired function of magnocellular pathway will lead to destabilization of binocular fixation, which leads to visual confusion: letters appear to move around. It has been found that binocular control of dyslexics is poor. Their eyes are unsteady when they are attempting to view small letters; hence, their vision is unstable and they tend to make visual reading errors [25].

Postmortem studies of dyslexic individuals have shown that magnocells (large neurons) of the lateral geniculate nucleus were disordered and 20% smaller than those of controls [26,27].

## 5. Remediation and Medication

• The frequency of learning disorders and the negative outcomes associated with them, namely, poor self-esteem, higher unemployment rates, and social difficulties make it imperative that professionals involved in providing medical care be active participants in all management strategies and treatment plans for affected children and adults [28].
• The primary use of medication for children with learning disabilities is to open for them a window of opportunity for education intervention. Medications such as methylphenidate, antidepressants such as Fluoxetine, and mood stabilizers such as lithium carbonate or valproic acid may directly enhance cognitive processes. These drugs are usually used because Attention Deficit and Hyperactivity Disorder coexist in 40% of the population of children with learning disabilities. Furthermore, affective disorders such as anxiety disorders, depression, mania or phobia may coexist with LDs. There is increasing evidence that in some children with LDs, subclinical epileptiform discharges do cause transient cognitive impairment without clinical seizures. In these cases, the use of valproic acid results in improvement in cognitive performance and this improvement is proportional to the reduction in epileptiform discharges [29].
• My review is focused on the nootropic drug piracetam and studies of its use in the management of learning disabled children.

## 6. Background

Dyslexia is the most frequently reported LD in literature concerning medical management. There is no one single unified theory that explains the etiology and neuropathology of dyslexia. Management of learning disabilities needs a multimodal approach to the child. This includes developing a relationship with the family, making recommendations regarding educational strategies, and discussing and using medications when appropriate [28,30,31].

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The nootropic drug, piracetam, which reached clinical practice in 1971, had proven efficacy in animal studies [32-35], acute stroke [36], rehabilitation of aphasia [37], and cortical myoclonus [38]. Those results encouraged additional research on piracetam's use in learning disabled children—the subject followed in this review.

## 7. Objectives

To review the studies and all research and case reports about the use of piracetam, a nootropic medication in the management of learning disabled children.

### Search strategy

I conducted a thorough search of MEDLINE, MEDSCAPE and PubMed and personally contacted many researchers, clinicians and pharmaceutical companies to collect studies. Any available reference lists of relevant articles were searched and authors were contacted when feasible to obtain reprints of prominent papers.

### Piracetam and dyslexia

Wilsher *et.al.* (1985) reviewed 13 experiments with piracetam; these were performed on different patient populations as well as on normal volunteers. Improvement in verbal learning, naming, sequencing, coding, tempo, vigilance, and reading were reported [39].

In 1976, Dimond and Brouwers had performed a well controlled double-blind experiment on young, normal volunteers who were university students. They found a significant improvement in verbal learning after 14 days of piracetam medication [40].

Three years later, Wilsher, Atkins, and Manfield conducted a double-blind study on 16 young adult dyslexics and 14 controls, using a 3-week administration of piracetam (4800 mg/day) and studied the effects upon verbal learning. The dyslexic's previous learning pattern was characterized by taking almost twice as long to learn the task and making three times as many forgetting mistakes as controls. After treatment, the piracetam group improved their verbal learning by 15% and their forgetting score was almost halved.

Simeon *et al.* in 1980 conducted his own experiment: the double–blind administration of 4800 mg/day of piracetam or placebo in 4-week sessions [40]. Simeon's sample consisted of 3 groups of 25 learning disabled boys aged 8 to 14 years who were at least one year behind their age in reading, spelling or arithmetic. There was uniformly significant neuropsychological improvement with amelioration of global judgment and memory [41].

Also in 1985, Wilsher, Atkins, and Manfield conducted an 8-week double-blind experiment on 46 dyslexic boys—42 with reading and spelling problems and 4 with only spelling difficulties. The subjects were 8 to 13 years old and of above average intelligence. The investigators' used doses of 3300 mg piracetam or placebo. The results showed substantial improvement of the treated patients in reading gain scores (Neale) and in rate and accuracy of reading (Neale Analysis of Reading Ability). The free writing test showed that the piracetam group's increase in number of words was twice that of the placebo group and their spelling mistakes decreased by 6.37% [39].

DiIanni and associates (1985) conducted a study by 6 investigators following a common protocol. Eligible patients were males between the ages of 8 and 13 years, 11months, with English as the primary language. There were 257 boys in all, of which 133 were treated with piracetam at a daily dose of 3300 mg and 124 were treated with matching placebo. Duration of the study was 12 weeks. Here again, there was a positive change in the speed of reading, with significant differences between treatment in favor of the piracetam-treated patients. A difference in digit span was observed, but not statistically significant between treatment groups [43]. Those results provide the same evidence as in Wilsher *et al.* (1985), that piracetam can increase the rate of reading in dyslexic children [39].

Improvement in auditory short-term memory with piracetam was also reported by Dimond and Brouwers in 1976 [40] and Wilsher *et al.* in 1979 [42].

Levi & Sechi (1987) studied 127 children (94 males and 33 females) between the ages 7½ years and 12½ years. The children were assigned oral drug treatment on a double-blind basis, half receiving 3200 mg of piracetam daily for 20 weeks, the other half receiving a matching placebo during the same period [44].

There was evidence of improvement the story-telling performance measure (long–term memory) in the piracetam group; a marked improvement in performance on the Anagram task was also noted in the medicated group. During this test, ever longer stimuli words were used in order to evaluate the meta linguistic skills of the child. DiIanni *et al.* had demonstrated in 1985 a very important correlation between the latter and the child's reading abilities. Children on piracetam made significant gains in reading accuracy [43].

The results of the initial study by Wilsher *et al.* [42] encouraged a collaborative multicenter larger study [45]. This was conducted by 5 investigators and included 225 children with a primary diagnosis of developmental reading disorder (DSM-III) who were between the ages of 7½ years and 12 years, 11 months, 112 of whom were treated with piracetam, while 113 were treated with a matching placebo. The duration of study was 36 weeks [42,45]. Results of the piracetam group showed improvement in the Gray Oral total passage score, which represents a global improvement in ability that combines reading accuracy and speed. Also there was a consistent improvement in reading comprehension shown by the significant effects upon both Gray and Gilmore comprehension scores.

Van Hout and Giurgea (1990) reported their double-blind controlled study of 36 right-handed dyslexic boys, aged between 8 years, 9 months and 12 years, 11 months [46]. The primary language of the children was French and the duration of study was 12 weeks. Children under 10 years of age in the treatment group received 1.5 g of piracetam a day and children over 10 years old received 3.3 g/day. The treated group read more words and had better accuracy level, as well as improved phonological word decoding skills. But the researchers did not find an increase of digit span as described by DiIanni *et al.* in 1985 and were unable to show any left hemisphere functional enhancement.

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## 8. Conclusions

There is increased interest in and knowledge about Learning Disabilities (including dyslexia). Multidisciplinary research is providing improved fundamental understanding of the nature of this disorder, especially since extensive genetic studies and genome-based screening have become available.

Great benefits have been gained from the safe and non-invasive functional magnetic resonance imaging (fMRI) of children: Positron Emission Tomography (PET), the alternative, is not recommended during childhood because of its use of isotopes. Learning disabilities are a major educational problem and a constant challenge to students, teachers, and researchers.

Children suffering from these disabilities must be identified as early as possible and directed to appropriate evidence-based remediation and medication, among which nootropic drugs should have a role.

The experience with piracetam has been reviewed. Continued research into the introduction of other drugs in this class is needed. Such drugs should be thoroughly investigated as to efficacy, safety, and duration of use before they are recommended.

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