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Piracetam in Developmental Reading Disorders: A Review

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This paper reviews the studies that have examined piracetam, the first of the nootropic drugs, as a treatment for developmental reading disorder. In various studies, 751 children have completed treatment in controlled double-blind trials using standardised tests of reading as outcome measures. Quantitative and qualitative review suggests that the findings are best interpreted as showing a statistical superiority of piracetam over placebo. Mechanism of action and clinical significance are discussed. The effect size is modest, but the drug is well tolerated and the balance of benefit over hazard is encouraging for future use.

Introduction

Development Reading Disorder (DRD) is characterised by a failure to learn to read, disproportionate to cognitive abilities, in spite of normal sensory equipment and adequate opportunities to learn (American Psychiatric Association, 1980). The concept is closely akin to that of specific reading retardation (Rutter & Yule, 1975). The causes are not entirely known, but biological contributions to the aetiology have been suggested by genetic evidence from twin and family pedigree studies (Pennington, 1990), by findings of localised cerebral hypoperfusion (Lou et al., 1984; 1989) and by post-mortem findings of architectonic anomalies in the cortex (Galaburda & Kemper, 1979; Galaburda, 1985). The outcome is not good, for affected people have persistent difficulties in literacy (Finucci 1986), and they are at risk for psychiatric disorders, especially disorders of conduct (Spreen, 1982).

Educational interventions are of limited value. Until recently, no psychological procedure was demonstrated to be helpful (Gittelman, 1983). The phonological sensitivity training methods of Bradley and Bryant (1983) are interesting, but not yet demonstrated as a treatment method for DRD. Stimulant medication has not been effective in trials conducted on children who do not show hyperactivity (Gittelman-Klein & Klein, 1976; Gittelman et al., 1983). New treatment methods, therefore, deserve attention.

The introduction of nootropic drugs, which are purported to improve memory and learning, raises the possibility that they might prove beneficial in DRD. The first developed drug in this class is piracetam (2oxo-1 pyrrolidine acetamide, trade name Nootropil) which is a cyclic derivative of gamma-aminobutyric acid (GABA). The exact mechanism of action of piracetam is unknown and discussed in Giurgea and Salama (1977) and Nicholson (1990).

Five double-blind controlled studies in normal adults have used tests of verbal learning and memory; in all the published studies piracetam was superior to placebo in verbal function (Mindus et al., 1976; Wedl & Suchenwirth, 1977; Wilsher et al., 1979; Hyde, 1980; Dimond & Brouwers, 1976). Dimond and Brouwers (1976) argued that improvements were seen chiefly in the abilities associated with left hemisphere function. They studied normal university students before and after 14 days of piracetam in a double-blind crossover protocol, applying measures that they had previously investigated in a "divided visual field" study of different hemisphere abilities (Dimond & Beaumont, 1973). Those measures revealed a significant drug-

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related increase in left hemispheric function whilst leaving bilateral tasks unaffected.

This paper reviews the effects of piracetam on DRD. After noting some particular methodological problems in this field of study, it summarises the results of studies to date and provides a critique of the methods adopted, the consistency and significance of results, and the frequency and severity of adverse effects.

Methodological Considerations

All trials of treatments for reading disabilities must reckon with some difficulties in methodology. The multiplicity of definitions of reading disability, and the unwillingness of some investigators to apply consistent quantitative criteria, can make it hard to compare results across studies. Clear description of subjects is needed, for general cognitive ability as well as reading skills. Outcome measures need to be sensitive, but usually are not. The point is that reading is, of course, a learned skill. No physical treatment can implant the skill; at best it can only make learning quicker and better. Any gain in the ability to learn will be only slowly and imperfectly reflected in measures of reading achievement, and outcome measures therefore need to record small changes reliably. By the same token, trials must be prolonged over a time scale long enough for learning to be measurable. In practice this should mean a period of several months extending over two or more school terms. Learning opportunities, ideally, should be held constant between treated and control groups.

Outcome measures should be of reading itself, rather than concentrating only on related abilities such as memory, since the neuropsychological bases are not yet fully elucidated. Multiple measures are necessary, since reading skill has many aspects. One must reckon at least with the accuracy and speed of reading aloud and the ability to understand what has been read. The reading of single words and of connected passages of text need separate assessment. No single test of reading is considered satisfactory for all purposes, and investigators accordingly tend to use more than one test of each function.

The use of multiple measures immediately allows the possibility of Type 1 errors if a change in any single test is interpreted as evidence of efficacy. One must therefore impose stringent criteria of statistical significance, or hope to see effects on several measures, or a consistent pattern of change across studies, before accepting changes as evidence of efficacy.

Review of Studies

Studies were identified from the published literature and from information from the manufacturer of piracetam about trials conducted, so a total coverage of completed studies is likely to have been obtained, but the existence of unpublished work cannot be entirely ruled out.

The criteria for including studies in this review were, first, that a double-blind placebo- controlled trial design had been employed (and this excluded some single-case studies); second, that the subjects had a developmental reading disorder (so that the studies mentioned above, which were based solely on normal volunteers, were excluded). Various words were used by the investigators to describe the problems of the young people investigated, including "dyslexia" and "specific learning disorders": all such terms were included in this review and the grounds for admission to the trials will be discussed.

The main characteristics of the investigations are presented in tabular form (Tables 1 and 2). Table 1 presents only those controlled studies in which the dependent measure for assessing outcome was proficiency in reading. Table 2 sets out the investigations in which outcome was gauged by neuropsychological tests believed to be relevant to ability to read.

The initial clinical study in dyslexia (Wilsher et al., 1979), involving 16 male dyslexic adolescents and 14 normal student volunteers in a 3-week double-blind trial of 4.8 g piracetam or placebo per day, found that dyslexics (and normals) treated with piracetam showed a decrease in the number of trials required to reach criteria in a rote verbal learning task, while after placebo both groups showed insignificant minor changes.

Another early study by Simeon et al. (1980) studied 14 'learning-disordered' boys in a 4-week double-blind crossover study of 4.8 g/day; they found a significant improvement in *global* evaluation of efficacy, but did not find any changes in learning or cognitive tasks. The lack of clinical effect may have been due to population heterogeneity, small numbers in each group, crossover effects, or the short duration of treatment. This same team reanalysed their results in light of their EEG