The Efficacy of the Use of RITALIN FOR HYPERACTIVE CHILDREN a Critical Evaluation

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Abstract

The literature concerning the efficacy of the use of methylphenidate hydrochloride (Ritalin) for hyperactive children has been reviewed. Twenty-two articles were evaluated for internal and external validity and statistical procedures. Of these studies, all failed to account for both the Hawthorne and Rosenthal effects as rival hypotheses. The statistical procedures in 17 of the studies were noted to be misused. After consideration of the many side effects of Ritalin therapy in combination with the poor evidence for its beneficial effects, efficacy for the use of the drug in the treatment of hyperactive children appears lacking. The fact that Ritalin is a sympathomimetic drug affecting accommodative facility has important implications for the optometric treatment of children who are medicated with this drug. Further clouding the efficacy of Ritalin use is the complex diagnostic guidelines for hyperactivity, most recently known as ADHD (Attention Deficit and Hyperactivity Disorder). It is concluded that alternative treatments such as behavioral programs and EEG biofeedback be investigated.

Key Words

Ritalin, methylphenidate hydrochloride, vision, learning problems, experimental design

During the past several years, I became aware of a continued and renewed interest in the use of Ritalin (methylphenidate hydrochloride) for children with learning problems. A recent report by Henig[1] stated that approximately one million children with learning problems are being given Ritalin daily. This motivated me to review a report that I had prepared in 1976. I also conducted a literature review of papers since 1976 and found another series of articles on Ritalin, many of which supported my initial reaction, that there was a lack of proven efficacy for the use of Ritalin for children with learning problems.

Further, since 1975, I have observed patients who have been given Ritalin and have found that it frequently creates an increase in hyperopia and a reduction of accommodative facility. This is apparently caused by the sympathomimetic effect of the drug. In this regard, I would appreciate receiving case histories from my optometric colleagues who have evaluated patients taking Ritalin. I believe that a compilation of the optometric findings for a large number of patients will be extremely useful in fully evaluating the efficacy of Ritalin.

A side benefit of reading this article is to give the reader a strategy for reviewing research articles by utilizing the same critique format as presented in the present paper and outlined in the Appendix.

The purposes of the present paper are to:

1. Overview the rationale and proposed mechanisms for the use of this drug;
2. Discuss the mechanism for the general and visual side effects of Ritalin;
3. Critically evaluate the Knights and Hinton study[2] (which the literature identifies as the basis for the use of Ritalin) according to the critique format in Appendix A;
4. Critically review the literature from 1963 to 1976 on this drug according to the format presented in Appendix A;
5. Use the same format to critically review the major studies from 1977 to 1989. The ambiguity in the term "hyperactive" will not be dealt with in this review since Bendix[3] has already discussed the topic in detail. Also, see Ullman and Krasner[4] for the effects of labeling on human behavior;
6. Call for optometric findings of patients taking Ritalin.

PHYSIO-PHARMACOLOGICAL MECHANISMS OF RITALIN

The rationale for the use of Ritalin management of hyperactive patients is somewhat complex. Ritalin has a sympathomimetic effect reportedly similar to the more popular amphetamines. The well-known amphetamine effect is as a stimulant. For a still unexplained reason, the stimulant effect is reported to suppress or reduce activity of hyperactive children. This is known as the "paradoxical effect." One possible explanation is that children who are labeled as hyperactive have a concomitant attention deficit. The sympathomimetic stimulation of Ritalin would then activate the anatomical structures responsible for attention, such as the reticular activating system and the nucleus locus coeroleus.[5] The result would then be to reduce the child's extraneous motor behavior and allow for increased higher level activity.

Another possible hypothesis is that the sympathomimetic effect stimulates centers such as the hippocampus and

amygdala, which have been reported to be responsible for learning and memory[6] and are sensitive to changes in the balance between parasympathetic and sympathetic nervous system activity.

An important consideration of sympathomimetic drugs is that their effects are usually diffuse on the sympathetic nervous system (SNS). This is caused by the many post-ganglionic fibers that innervate a myriad of body structures.[7] Thus, if the balance in some brain structures involved in learning and behavior is altered toward increased SNS activities, so will other structures in the brain and other parts of the body. This is the mechanism involved in the drug's side effects. In the case of Ritalin, the list of known side effects is long, and many of the effects severe. A complete discussion of the side effects are presented later in the paper and are summarized in Table 3.

RITALIN AND VISION

Historically and particularly more recently, there has been strong evidence documenting the SNS activity involving accommodation. Gilmartin[8] authored an extensive review of the SNS activity in accommodation. The mechanism is negative accommodation and can be defined as a reduction in the dioptrics of the eye caused by a flattening and thinning of the lens as a result of dilation of the ciliary muscle. It appears that the SNS innervation to the accommodative mechanism involves both alpha and beta fibers.[9]

One finding that appears consistent in research reports is that there is a reduction of the amplitude of accommodation with the administration of a sympathomimetic.[10,11]

Clinicians often find a reduced amplitude of accommodation and/or an increase in hyperopia in children undergoing Ritalin therapy. Certainly, if this is typically the case, then Ritalin would be contraindicated for hyperactive children with learning problems. It is documented in the optometric literature that a decreased amplitude of accommodation or increased hyperopia are correlated with learning problems and not learning enhancement. A review of this literature[12] strongly indicates that a decreased amplitude of accommodation or increased hyperopia are correlated with poor academic performance.

HISTORY OF THE USE OF RITALIN

A review of the major articles from 1963 to 1976 concerning the efficacy of Ritalin for hyperactive children reveals that the major support for using Ritalin is a study by Knights and Hinton.[2] The study is cited in Goodman and Gilman,[13] a highly regarded pharmacology textbook, as substantiating the beneficial effects of Ritalin in hyperactive children. Most of the other studies reviewed in this paper similarly refer to the Knights and Hinton[2] report as the standard.

EVALUATION OF THE KNIGHTS AND HINTON STUDY

In summary,[2] a double-blind design was used to determine the effects of Ritalin on motor skills and behavior of children with learning problems. There were 20 children in the treatment group and 20 in the placebo group. The pool of subjects ranged in age from 8 to 15 years with a mean of 10.5 years (s=1.6). The children were tested for motor skills and behavior three times: 1. five and one-half months prior to the beginning of the study, 2. at the beginning of the study, and 3. six weeks after the beginning of the study.

This study was experimental in nature and the authors reported finding a relationship between the independent variable, methylphenidate hydrochloride (Ritalin), and the dependent variables, motor skills and behavior of children with learning problems.

An evaluation of the Knights and Hinton study follows, according to the research critique format in the Appendix.

The threats, alternate hypotheses, to the internal validity of the study are discussed below.

Experimental Mortality Two subjects were lost from the control (placebo) group and one subject was lost from the experimental group. Since the N for each group was 20, the differential loss from the matched groups was not accounted for in the data analysis.

Hawthorne and Rosenthal Effects The authors admitted the fact that these effects were not controlled by the double-blind design of the experiment (see Appendix; A, 9 and 10).

Statistical Analysis Age and Weschler Intelligence for Children (WISC) scores were not normally distributed and consequently did not fulfill the assumptions for using parametric statistics. WISC and Bender- Gestalt test scores are on ordinal scales and consequently did not fulfill the criteria for using parametric statistics. Considering that these violations tend to increase Type I Error (rejection of the null hypothesis), the 0.01 level of confidence should be adopted.[14] With the 0.01 level, only nine of the 61 F tests were significant. Among the non-significant F's were the main drug effects.

The threats to the external validity of the experiment were found to be the following:

Describing the Independent Variable Explicitly The children's parents administered Ritalin or placebo. No reliability or validity of parental reports were offered by the authors.

Measurement of the Dependent Variable The terms motor skills and behavior were only defined by the few tests administered during the study.

Interaction of Time of Measurement and Treatment The reported improvement in test scores were found six weeks after the pre-test and not on the six-month post-test.

Summary

Due to the many threats to the internal and external validity of the Knights and Hinton experiment, their results must be viewed with skepticism. Another experiment should be performed eliminating the defects in internal and external validity in order to more scientifically examine the efficacy of Ritalin with hyperactive children.

REVIEW OF THE LITERATURE ON RITALIN AND HYPERACTIVE CHILDREN

The major articles from 1963 to 1976 were reviewed and are presented in Table 1.

Initially I planned to evaluate each article for both internal and external validity. However, after reviewing the 15 articles, it appeared unnecessary to consider the external validity. In each study there were sufficient rival hypotheses to the internal validity to render generalization meaningless. As can be readily seen from Table 1, all studies failed to account

Table 1
The Internal Validity of Ritalin Studies
1963 - 1976

	History	Maturation	Testing	Instrumentation	Statistical Regression	Differential Selection	Experimental Mortality	Selection-Maturation Interaction	Hawthorne Effect	Rosenthal Effect	Statistical Analysis
Christensen and Sprague[31]				x		x			x	x	
Cohen et al.[19]				x					x	x	
Conners and Eisenberg[20]							x		x	x	x
Conners et al.[21]							x		x	x	x
Ellis et al.[28]									x	x	x
Porges et al.[54]				x					x	x	x
Rappaport et al.[22]				x					x	x	x
Schnackenberg and Bender[23]									x	x	x
Sleator et al.[27]							x		x	x	
Sprague and Sleator[55]									x	x	x
Spring et al.[24]									x	x	
Sroufe et al.[29]									x	x	x
Sykes et al.[25]							x		x	x	x
Sykes et al.[26]									x	x	x
Sykes et al.[56]							x		x	x	x

x: Indicates that this alternate hypothesis can account for the treatment effect.

for the Rosenthal and Hawthorne effects. The combination of these effects on psychological experiments have been discussed in detail by Orne[15,16,17] and Ullman and Krasner.[4] Failure to account for these effects is critical because the primary purpose of a drug study is to test whether the drug effect is different from no drug or a placebo. The Hawthorne and Rosenthal effects can be eliminated with careful experimental control. In the double-blind studies on Ritalin, the side effects of the children under the medication were obvious and easily noted by parents and experimenters, leading to the Rosenthal effect. The children then became aware of their medication condition from their parents or experimenters, leading to the Hawthorne effect. Such citations were given in the following articles: Aman and Sprague;[18] Cohen, Douglas, and Morgenstern;[19] Conners and Eisenberg;[20] Conners, Eisenberg, and Sharpe;[21] Knights and Hinton;[2] Rappaport et al.;[22] Schnackenberg and Bender;[23] Spring, Greenberg, Scott, and Hopwood;[24] Sykes, Douglas, Weiss, and Minde;[25] and Sykes, Douglas, and Morgenstern.[26] Some of the studies were neither single-blind nor double-blind, e.g., Sleator, von Neumann, and Sprague.[27] Sleator et al.[27] also did not use a control group in their experiment. Ellis, Witt, Reynolds, and Sprague[28] also did not utilize a control group or a control methodology such as a single subject design.

The next most common alternate hypothesis in the experiments was the statistical analysis. In the statistical analysis frequent errors were made by using parametric tests on ordinal data. For example, Sroufe, Sonies, West, and Wright[29] utilized a t-Test on median scores from a non-normal distribution. The violation of the statistical validity of not abiding by the correct assumptions of the t-Test has been described in detail.[30]

Other rival hypotheses included experimental mortality, differential selection between the experimental and control groups, and instrumentation. Problems in experimental mortality existed where the experimenter did not account for subjects who dropped out of the experiment. In one study, Christensen and Sprague,[31] there was a differential selection between the drug and placebo groups which could account for the results of the experiment. Instrumentation difficulties were illustrated by Cohen et al.[19] In these studies the testing methods for the dependent variable were not shown to be valid or reliable.

REVIEW OF ARTICLES FROM 1977 TO 1989

As opposed to the earlier publications, there is no longer unanimous and unreserved approval of the efficacy of Ritalin.[32] For a thorough review of recent articles see Henker and Whalen.[33]

A review similar to the earlier articles was conducted, using the critique format as discussed in the Appendix, and is presented in Table 2.

One new facet to the Ritalin reports is that they are typically conducted accord-

Table 2
The Internal Validity of Ritalin Studies
1977 - 1989

	History	Maturation	Testing	Instrumentation	Statistical Regression	Differential Selection	Experimental Mortality	Selection-Maturation Interaction	Hawthorne Effect	Rosenthal Effect	Statistical Analysis
Brown and Sexson[37]				x					x	x	x
Eichiseder[34]	x	x	x	x	x		x		x	x	
McBride[35]			x	x					x	x	x
Rapport et al.[35]			x						x	x	x
Sebrechts et al.[38]			x	x					x	x	x
Ullman and Sleator[57]			x	x					x	x	x

x: Indicates that this alternate hypothesis can account for the treatment effect

ing to a crossover experimental design. Basically, the design uses the subject as his own control, eliminating the need for a matched control group. In addition, the drug condition is randomly mixed with a placebo condition. A pre-test with a post-test for each of the drug and placebo conditions is a standard feature of the crossover design. With the exception of Eichlseder,[34] a case study report, all papers reviewed utilized the crossover design. Because of the repeated measurement feature of the crossover design, these studies are flawed due to the difficulty of repeating the same test multiple times. However, the most serious flaw in experimental design is the use of rating scales without determining interobservor reliability. In fact, only one of the studies[35] reported a measure of interobservor reliability. As with the earlier reports, the review of the recent articles revealed difficulties controlling for the Hawthorne and Rosenthal Effects, as noted in Table 2. Once again the difficulty arose from the numerous side effects noticed by the child and the parents and teachers. For example, "In this study, objectivity was lessened for a few parents because the decreased appetite associated with methylphenidate led them to suspect which capsules contained the drug. Teachers, however, were not generally aware of the decreased appetite in those children and hence were not able to tell which capsules the child was taking unless his function changed."[36] Brown and Sexson[37] reported an increase in the side effects with increased administration of the drug versus placebo conditions. As noted earlier, violations such as this negate the double-blind nature of an experiment and allow the effects of bias to become operative.

As shown in Table 2, the last threat to the internal validity of these reports was that of Statistical Analysis. Except for the case studies by Eichlseder,[34] all the studies utilized rating scales and parametric statistics for their analysis. The difficulty in the use of parametric statistics with rating scales is that parametric statistics assume that there is at least an equal interval between scores. With rating scales, the interval is only one of order. For example, the finishing positions in a race only provide information about the order of the finish and not the interval between the racers.

SIDE EFFECTS

The fact that the above studies do not show the efficacy of Ritalin for helping hyperactive children should be apparent to the skeptic and make a skeptic out of the believer. But the argument should not stop at this point. The weak evidence for the value of Ritalin must now be viewed in the light of its reported side effects. The results of the literature review are presented in Table 3. The side effects are listed alphabetically.

The side effects enumerated in Table 3 are considerable. The fact that they are listed with documentation by the Food and Drug Administration is significant. One report of side effects was not shown in the chart.. Golden[39] reported a case of a 9-year-old boy developing Gilles de la Tourette's Syndrome (malady of multiple tics) after receiving 10 mg of Ritalin twice a day for eight weeks. Although the authors cautioned about making any cause and effect relationship between Ritalin and the syndrome, the implications are clear. The biochemical actions that create the "paradoxical" effect of Ritalin are not known, and Ritalin should be used with careful consideration. In addition, the long-term effects of Ritalin on children have not been evaluated to date; therefore, the list in Table 3 are only short-term effects, i.e., one year or less.

Table 3
Side Effects of Ritalin*
(Listed in alphabetical order)

Abdominal Pain
Accommodative Disturbances
Alopecia
Angina
Anorexia
Blood Pressure Changes
Blurred Vision
Cardiac Arrhythmia
Catatonic Withdrawal
Dizziness
Drowsiness
Dryness of the Mouth
Dyskinesia
Growth Inhibition
Hallucinations
Headache
Hypersensitivity
Insomnia
Mydriasis
Nervousness
Nausea
Palpitations
Psychic Dependence
Pulse Changes
Tachycardia
Weight Loss

* These adverse reactions are listed in one or more of the following:
AMA Drug Evaluations[58]
Kastrup and Schwach[59]
Lewis[60]
Lucas and Weiss[61]
Osol and Pratt[62]
Physician's Desk Reference[63]
Safer, Allen, and Barr[64]
Schnackenberg[65]
Weil[66]

SUMMARY

I have questioned the efficacy for the use of Ritalin in children who have been labeled as hyperactive. Some previous literature reviews have not been critical of the nature of the research on Ritalin.[40,41,42] However, other reviewers have pointed out that the research on Ritalin for hyperactive children is highly suspicious.[3,43]

The present review of the literature on the effectiveness of Ritalin has evaluated 16 major articles on the criteria of internal and external validity.[44] All the studies failed to meet these criteria by possessing viable alternate hypotheses to account for the experimental effects.

Therefore, at this time there is scant evidence for the use of Ritalin in hyperactive children to produce improved learning. This lack of evidence is consequential because of the many side effects produced by Ritalin administration. The title of Bendix's[3] article would seem highly appropriate in the light of these factors. Her title is, "Drug Modification: A Form of Chemical Violence Against Children?" Bendix's caution had apparently not been heeded, as illustrated by the March 1976 issue of the *Journal of Learning Disabilities*. In this issue, Murray[45] concluded his review on Ritalin by emphasizing the importance of the classroom teacher in initiating stimulant therapy such as Ritalin. Most recently, however, the Ritalin controversy has reappeared in a series of articles in *The New York Times*. In a Letter to the Editor, Kline[46] concludes that:

> "Children for whom it is prescribed not only are in danger

of serious side effects, but also are being deprived of accurate diagnosis and appropriate treatment."

As noted in Table 3, one of the reported side effects of Ritalin is mydriasis as a result of its sympathomimetic effect. In view of recent reports of the sympathetic nervous system innervation to the ciliary muscle,[8] Ritalin must similarly affect accommodation. If Ritalin dilates the pupil, it could similarly cause a dilation of the ciliary muscle with increased hyperopia and a reduction in accommodative facility. This limits the child's ability to visually attend, which is contrary to the one of the inherent target behaviors of Ritalin.

CONCLUSION

There appears to be scant scientific data that supports the use of Ritalin with hyperactive children. Although there have been reports of hyperactive children being helped by the use of Ritalin, the cause and effect relationship is difficult to understand.

The manufacturer of Ritalin, CIBA-Geigy Pharmaceutical Company has been accused of effectively creating a market for this drug. For a detailed account of CIBA's Ritalin campaign, see Messinger.[47] It is recommended, therefore, that alternative treatments, other than Ritalin, be considered in the treatment of hyperactive children.

Since the late 1970s and early 1980s, two alternative strategies for the treatment of hyperactive children have developed: 1. behavioral treatment, and 2. electroencephalographic (EEG) biofeedback. One of the earliest descriptions of a behavioral approach was reported by Ayllon, Layman, and Kandell[48] in 1975. To illustrate the increase in interest in alternatives to Ritalin, a recent Medline literature search revealed 12 articles on the behavioral approach since 1989.

EEG biofeedback for children with hyperactivity was described in 1984 by Lubar and Lubar.[49] The basis for their treatment is to reduce the high amplitude theta brain wave and increase activity of the high alpha and beta frequencies. The popularity of the EEG training was demonstrated at the 1991 Association for Applied Psychophysiology and Biofeedback Meeting,[50] where several workshops were devoted to the topic. Hopefully more publications will report on the efficacy of biofeedback applications to hyperactive children.

Clouding the use of Ritalin even further is the current problem in the diagnosis of children with hyperactivity (now known as ADHD, Attention Deficit and Hyperactivity Disorder). According to Wolraich et al.'s[51] and Barkley's[52] authoritative texts, the guidelines for ADHD diagnosis are difficult to apply and many children receiving Ritalin have not received the proper diagnostic evaluation.

As an interesting postscript I would like to quote an article that appeared in the *Washington Post*:[53]

> "Baltimore, Sept. 19, 1988 -- Stephen E. Breuning, a nationally known drug therapy researcher, pleaded guilty in federal court today to falsifying medical studies once considered significant in shaping drug treatment policy for mentally retarded children.
>
> "In the rare academic fraud case, the 36-year-old psychologist pleaded guilty to two counts of submitting phony research results to support applications for more than $200,000 in grants from the National Institute of Mental Health in Bethesda in 1983 for continued studies on the effect of the controversial drugs Ritalin and Dexedrine on retarded children."

APPENDIX

FORMAT FOR A CRITIQUE

In order to produce a reasonable review of the literature on Ritalin, the following format was utilized. The articles were reviewed with respect to the criteria for internal and external validity of experimental design.[44,67,68]

A. INTERNAL VALIDITY

Internal validity is the measure of the effect of the experimental treatment, i.e., did the treatment produce the reported results? The following represent the extraneous variables, which, if not controlled, become threats to the internal validity of the experiment.

1. History
   Certain events may produce the differential results between the first and second measurements. An example is an opinion poll of confidence in government taken before and after the Watergate scandal.
2. Maturation
   The influence of physiological and psychological changes may produce differential results between the first and second measurements. For example, one would expect a 7-year-old to differentially improve his reading skills proportionally more than a 21-year-old during a six-month training session.
3. Testing
   The effect of taking the same test before and after treatment may produce an increased performance independent of the treatment.
4. Instrumentation
   The results of the experiment may be due to faulty instrumentation or poor calibration of a properly functioning instrument.
5. Statistical Regression
   If subjects are selected on the basis of extreme scores, one would expect the highest scores and the lowest scores to regress toward the mean of the distribution.
6. Differential Selection of Experimental and Control Groups
   If the groups are not matched, a difference in post-test scores may be a result of the selection bias and not the experimental treatment.
7. Experimental Mortality
   The difference between the post-test scores between the experimental and control groups may be due to a differential loss of subjects from the matched groups.
8. Selection-Maturation Interaction
   If there is a biased sampling to produce the experimental and control groups, there may be a difference in post-test scores which is not due to the treatment. This category is the interaction of numbers 2 and 6 above.
9. The Hawthorne effect occurs if a subject believes that his performance is supposed to improve during the experiment.
10. The Rosenthal effect occurs if the experimenter believes that certain subjects are supposed to improve during the experiment. The Rosenthal effect has also been called the experimenter effect or the Pygmalion effect.

B. EXTERNAL VALIDITY

External validity provides an index for generalization of the experimental results. There are two major categories of threats to the external validity of an experiment, population validity and ecological validity. The population validity refers to the selection of the sample or, in other words, factors relating to the subjects. Ecological validity refers to the factors other than those concerned with the subject. While Bracht and Glass[44] have described 12 factors to control when considering external validity, only three ecological threats will be discussed.

1. Describing the Independent Variable Explicitly

   In the drug studies that have been reviewed, the independent variable was the amount of Ritalin that was ingested. It should be noted that only under the most controlled conditions could all the subjects ingest the exact amount of the medication that they were required to take.

2. Measurement of the Dependent Variable

   The dependent variable in the Ritalin studies include motor skills and attention, which can only be measured indirectly.

3. Interaction of Time of Measurement and Treatment

   A difference between the experimental and control groups may be found immediately after the treatment; but not on subsequent tests of the dependent variable.

In addition to evaluating the articles for the internal and external validity, the statistical procedures in each study were evaluated. Statistical considerations emphasized the employment of the proper assumptions for the statistical procedure with particular reference to problems of distribution[69] and scales.[70,71]

The critique format utilized in this paper incorporated consideration of internal and external validity and evaluation of statistical procedures. The format, adopted from McKay,[72] is outlined below.

OUTLINE OF A CRITIQUE

I. Preliminary Considerations
   A. The method by which the study was conducted--experimental or correlational.
   B. Was or was not an empirical relationship established by the investigator. Assume alpha to be significant at equal to or less than 0.05.
      1. Identify the independent variable
      2. Identify the dependent variable

II. Internal Validity (see Campbell and Stanley)[67]

   Rival Hypothesis–Plausible or Implausible–Brief Statement

   A.
   B.
   C.

III. External Validity (see Bracht and Glass)[44]

   Rival Hypothesis–Plausible or Implausible–Brief Statement

   A.
   B.
   C.

IV. Summary
   A. State of knowledge as a result of the study
   B. Recommendations

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