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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

'00 CV 1839 E (CGA)

TODD D. VESS, a Minor, by DEBORAH VESS, his Guardian ad Litem, individually, on behalf of those Similarly Situated and on behalf of the General Public of the State of California,

Plaintiffs,

v.

CIBA-GEIGY CORP. USA; NOVARTIS PHARMACEUTICALS CORP.; CHILDREN AND ADULTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (CHADD); AMERICAN PSYCHIATRIC ASSOCIATION, and DOES 1 through 100, inclusive,

Defendants.

CASE NO.

CLASS ACTION COMPLAINT FOR VIOLATION OF THE CONSUMER LEGAL REMEDIES ACT [CALIFORNIA CIVIL CODE §1750 et seq.];

and

COMPLAINT FOR RESTITUTION AND INJUNCTIVE RELIEF UNDER CALIFORNIA BUSINESS AND PROFESSIONS CODE §17200 AND §17500

and

DEMAND FOR JURY TRIAL

Individual and representative Plaintiff TODD D. VESS, by and through DEBORAH VESS as his Guardian ad Litem ("Plaintiff"), on behalf of the general public on behalf of those similarly situated,

alleges on personal knowledge those facts which pertain to the named Plaintiff or to his attorneys and further allege on information and belief as follows:

JURISDICTION AND VENUE

1. This Court has jurisdiction over this action pursuant to 28 U.S.C. §1332 because the amount in controversy exceeds Seventy-Five Thousand dollars ($75,000.00) and because there is complete diversity of citizenship between plaintiff and all defendants.

2. Venue is appropriate pursuant to 28 U.S.C. §1391.

3. At all relevant times, Defendants have done and continue to do business in the State of California and County of San Diego. They have made contracts to be performed in whole or in part in California. Defendants' products have been manufactured, tested, sold, offered for sale, supplied or placed in the stream of commerce in California. In the course of business, Defendants have materially participated with other Defendants in performing the acts described above, while knowing that Ritalin was dangerous and substantially certain to cause injury to Plaintiff and others similarly situated. They have received and continue to receive substantial compensation and profits from the sale of Ritalin in California and San Diego County. Defendants have made material omissions and misrepresentations in California. The wrongful acts and conduct, in furtherance of a conspiracy, are the basis of the claims that have occurred and continue to occur in California and San Diego County.

PARTIES

A. **Plaintiff (and Those Similarly Situated)**

4. TODD D. VESS, individually, through his Guardian ad Litem, DEBORAH VESS, is a minor who resides in the State of California, County of San Diego and County, and appears individually with respect to all causes of action, and also appears on behalf of those individuals similarly situated with respect to the First Cause of Action.

B. **Plaintiff (and the General Public)**

5. With respect to the Second and Third Causes of Action, plaintiff, a resident of the State of California, brings this action pursuant to California Business and Professions Code §17204, individually and as a private attorney-general on behalf of the members of the general public of California.

6. Plaintiff was prescribed, and purchased and ingested, the drug Ritalin in June, 1994, when he was nine years of age.

C. Defendants

7. Defendant CIBA-GEIGY CORP. USA is a corporation with its principal place of business in New Jersey and its corporate headquarters in the State of New York. It may be served through its registered agent in the state of California. The Prentice-Hall Corporation System, Inc., 2730 Gateway Oaks Drive, Suite 100, Sacramento, California 95833. This defendant has, at all times material hereto, transacted substantial and continuous business in the State of California.

8. Defendant NOVARTIS PHARMACEUTICALS CORP. is a corporation with its principal place of business and corporate headquarters in New Jersey. It may be served through its registered agent in the State of California. Corporation Service Company, 2730 Gateway Oaks Drive, Suite 100, Sacramento, California 95833. This defendant has, at all times material hereto, transacted substantial and continuous business in the State of California.

9. Defendant CHILDREN AND ADULTS WITH ATTENTION-DEFICIT / HYPERACTIVITY DISORDER (CHADD) is an unincorporated association with its principal office in Maryland. It may be served by serving its registered agent in California. Larry Komar, 1104 East Walnut Creek, Covina, California 91724. This defendant has, at all times material hereto, transacted substantial and continuous business in the State of California.

10. Defendant AMERICAN PSYCHIATRIC ASSOCIATION is a nonprofit corporation with its principal place of business in Washington, D.C. It may be served by serving its registered agent in California. Parascorp Incorporated, 1130 K Street, Suite LL60, Sacramento, California 95814. This defendant has, at all times material hereto, transacted substantial and continuous business in the State of California.

11. Plaintiff is informed and believes and thereon alleges that at all times herein mentioned, the true names and capacities, whether individual, corporate, associate or otherwise of defendants DOES 1 through 100, inclusive, are unknown at this time to plaintiff who therefore sues said defendants by such fictitious names. Plaintiff is informed and believes and thereon alleges that each of the defendants designated herein by such fictitious names were involved in the distribution,

manufacturing, promotion and/or sale of Ritalin, and were in some way legally responsible for the events and happenings herein referred to which were a legal cause and substantial factor in bringing about injuries and damages to plaintiff as alleged. Plaintiff will amend this complaint to allege the true names and capacities of the DOE defendants when ascertained.

FACTUAL ALLEGATIONS COMMON TO ALL COUNTS

12. Ritalin is a psycho stimulant drug. It is the trade name for a pharmacological substance known as methylphenidate. Methylphenidate, and therefore Ritalin, are "Class II" or "Schedule II" controlled substances under the Controlled Substance Act. See 21 U.S.C. §812; 21 C.F.R. §1308.12.

13. From approximately 1955 through 1995, the exclusive or primary manufacturer and supplier of Ritalin in this country was defendant Ciba-Geigy Corp., USA ("Ciba"). In 1996, Ciba merged with Sandoz Pharmaceuticals Corp. to become defendant Novartis Pharmaceutical Corp. ("Novartis"). Upon information and belief, Novartis is presently, and has been since 1996, the sole or primary manufacturer and supplier of Ritalin in the United States. Ciba, however, continues as a separate corporate entity. For ease of reference, defendants Ciba and Novartis are sometimes referred to in this complaint as "Ciba/Novartis."

14. Ciba/Novartis has manufactured, marketed and sold Ritalin since approximately 1955. The product was promoted, beginning in the 1960's, by Ciba as an antidepressant "which brightens moods and improves performance." Defendant also claimed effectiveness for depression, chronic fatigue and psychoneurosis. From 1955 until the late 1970's, Ciba aggressively sought applications and markets for Ritalin in an effort to boost sales and profits.

15. Ciba/Novartis, in combination with the defendant doctors and the American Psychiatric Association (APA), planned, conspired, and colluded to create, develop, promote, and confirm the diagnoses of Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) in a highly successful effort to increase the market for its product Ritalin. Due to the concerted efforts of these parties, Attention Deficit Disorder was first listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980. The DSM recognized ADHD as "diagnosis" in 1987.

16. The DSM is a widely used and disseminated compendium of psychiatric diagnoses. Listing of a "diagnosis" in the DSM provides an official-seeming, medical imprimatur to a particular set of symptoms or behaviors that may, in fact, be entirely normal. A new official "diagnosis" in the DSM, however, generates vast numbers of new prescriptions, increased insurance coverage, and great public attention.

17. In addition to its actions and involvement with the creation of the ADD and ADHD diagnoses, Ciba/Novartis took steps to promote and dramatically increase the sales of Ritalin by way of the following:

a. Actively promoting and supporting the concept that a significant percentage of children suffer from a "disease" which required narcotic treatment/therapy;

b. Actively promoting Ritalin as the "drug of choice" to treat children diagnosed with ADD and ADHD;

c. Actively supporting groups such as Defendant CHADD, both financially and with other means, so that such organizations would promote and support (as a supposed neutral party) the ever-increasing implementation of the ADD/ADHD diagnosis as well as directly increasing Ritalin sales;

d. Distributing misleading sales and promotional literature to parents, schools, and other interested persons in a successful effort to further increase the number of diagnoses and the number of persons prescribed Ritalin.

18. Ciba/Novartis deliberately, willfully, intentionally, and negligently promoted the diagnosis of ADD/ADHD and sales of Ritalin through its promotional literature and through its training of sales representatives. In so doing, despite knowledge of such problems and/or adverse reactions, Defendants willfully failed to address or provide adequate information to consumers, doctors, and/or schools concerning the many significant hazards of methylphenidate use and prescription, including, but not limited to, the following:

a. Cardiovascular problems, including palpitations, tachycardia, hypertension, arrhythmias, chest pain and cardiac arrest;

b. Central nervous system problems, including psychosis with hallucinations,

excessive brain stimulation (convulsions), drowsiness, confusion, insomnia, agitation, anxiety, irritability, nervousness, dysphoria, impaired cognitive test performance, dyskinesia, depression, and zombie-like constriction of affect and spontaneity;

c. Gastrointestinal problems, including anorexia, nausea, vomiting, stomach ailments, dry mouth, and constipation;

d. Pituitary dysfunction, including growth hormone and prolactin disruption, weight loss, growth suppression, growth retardation, anemia, exfoliate dermatitis, leukopenia, etc.

19. Despite information in the medical and scientific literature concerning these side effects of Ritalin use, Defendants failed in all respects to advise potential consumers, doctors, and/or schools, teachers or other interested parties of the nature and extent of such side effects. Furthermore, Defendant CHADD similarly failed to provide adequate information to interested parties concerning the nature and extent of potential side effects.

20. In addition, Ciba/Novartis continuously misrepresented to the consuming public, physicians and other interested parties, the efficacy of the drug Ritalin, without ever advising such persons that Ritalin usage would not improve academic performance and/or have any long term effect on the symptoms associated with ADD and/or ADHD.

21. Defendant American Psychiatric Association ("APA") conspired, colluded and cooperated with the other Defendants to facilitate and encourage the development and acceptance of diagnosis of ADD (1980) and ADHD (1987). While so doing, the APA received and accepted financial contributions from Ciba as well as other members of the pharmaceutical industry, which donations and contributions directly effected and caused APA to make every effort possible to support and confirm a new medical "diagnosis" for which a stated treatment would be methylphenidate, i.e., Ritalin. In so doing, Defendant APA aided, abetted and promoted the concept of Ritalin therapy for treatment of the vast numbers of children who began to be diagnosed with ADD and ADHD, pursuant to the APA's recommendations and support for the diagnosis.

22. The interrelationship between the drug industry and the APA caused and contributed

disruption, weight loss, growth suppression, growth retardation, anemia, exfoliate dermatitis, leukopenia, etc.

e. Misrepresenting to the consuming public, physicians and other interested parties, the efficacy of the drug Ritalin, without ever advising such persons that Ritalin usage would not stimulate or improve academic performance and/or have any long term effect on the symptoms associated with ADD and/or ADHD.

f. Facilitating the creation of a new diagnoses in the DSM.

29. Despite information in the medical and scientific literature concerning these side effects of Ritalin use, Defendants failed in all respects to advise potential consumers, doctors, and/or schools, teachers or other interested parties of the nature and extent of such side effects. Furthermore, Defendant CHADD similarly failed to provide adequate information to interested parties concerning the nature and extent of potential side effects.

30. The interrelationship between Ciba/Novartis, the drug industry as a whole, and the APA caused and contributed to the APA's assistance, support, aid, and collusion with Ciba/Novartis in creating a novel medical "diagnosis" that could be, and ultimately was, applied to a large percentage of children in the United States, and for which the APA, in combination with other defendants, continued and presently continue to promote the prescription, use and sale of Ritalin.

CLASS ACTION ALLEGATIONS
By Plaintiff on Behalf of All Others Similarly Situated
(Relating to Count One - Violation of California Civil Code § 1750 *et seq.*)

31. Plaintiff brings this Class action, individually and on behalf of others similarly situated, as a Class action pursuant to Federal Rule of Civil Procedure, Rule 23 and Section 1781 of the California Civil Code. The Class which Plaintiffs seek to represent is:

The class shall be composed of all California residents who purchased and/or ingested the drug Ritalin.

32. Specifically excluded from the Plaintiff Class are Defendants herein, any entity in which any of the Defendants has a controlling interest, any officers, directors or employees of any of the Defendants and legal representatives, heirs, successors, and assignees of any of the Defendants. Also excluded are any federal, state or local entities.

performance of those acts, in concert, to further the agreement. The conspiracy began as early as the 1950s and continues to the present. Defendants and each of them knowingly and willfully entered into and pursued a common course of conduct, by agreement with the other Defendants and third parties, to commit all or part of the unlawful acts alleged herein. Such unlawful acts were committed intentionally, knowingly, maliciously and without legal justification or excuse.

28. All Defendants conspired, combined and colluded to promote and dramatically increase the sales of Ritalin by way of the following:

a. Actively promoting and supporting the concept that a significant percentage of children suffer from a "disease" which required narcotic treatment/therapy;

b. Actively promoting Ritalin as the "drug of choice" to treat children diagnosed with ADD and ADHD;

c. Distributing misleading sales and promotional literature to parents, schools and other interested persons in a successful effort to further increase the number of diagnoses and the number of persons prescribed Ritalin;

d. Deliberately neglecting to address or provide adequate information to consumers, doctors, and/or schools concerning the many significant hazards of methylphenidate use and prescription, including, but not limited to, the following:

i. Cardiovascular problems, including palpitations, tachycardia, hypertension, arrhythmias, chest pain and cardiac arrest;

ii. Central nervous system problems, including psychosis with hallucinations, excessive brain stimulation (convulsions), drowsiness, confusion, insomnia, agitation, anxiety, irritability, nervousness, dysphoria, impaired cognitive test performance, dyskinesia, depression, and zombie-like constriction of affect and spontaneity;

iii. Gastrointestinal problems, including anorexia, nausea, vomiting, stomach ailments, dry mouth, and constipation;

iv. Pituitary dysfunction, including growth hormone and prolactin

33. This action is brought and may properly be maintained as a Class action pursuant to Federal Rule of Civil Procedure 23. The community of interest in the litigation is well defined and the proposed Class is easily ascertainable. This action satisfies the numerosity, commonality, typicality, adequacy, predominance and superiority requirements of this provision. In addition this action may be brought under California Civil Code § 1781.

34. Numerosity of the Class. The Class is so numerous that the individual joinder of all Members is impractical under the circumstances of this case. While the exact number of Class Members is unknown to Plaintiff at this time, Plaintiff believes that at a minimum, there are thousands of Class Members located throughout the State of California.

35. Common Questions Predominate. Common questions of law and fact exist as to all Members of the Class and predominate over any questions affecting only individual Members of the Class. These common legal and factual questions arise from various issues, which do not vary among Class Members:

(a) All Defendants conspired, combined and colluded to promote and dramatically increase the sales of Ritalin by way of the following:

i. Actively promoting and supporting the concept that a significant percentage of children suffer from a "disease" which required narcotic treatment/therapy;

ii. Actively promoting Ritalin as the "drug of choice" to treat children diagnosed with ADD and ADHD;

iii. Distributing misleading sales and promotional literature to parents, schools and other interested persons in a successful effort to further increase the number of diagnoses and the number of persons prescribed Ritalin;

iv. Deliberately neglecting to address or provide adequate information to consumers, doctors, and/or schools concerning the many significant hazards of methylphenidate use and prescription, including, but not limited to, the following:

(A) Cardiovascular problems, including palpitations, tachycardia, hypertension, arrhythmias, chest pain and cardiac arrest;

(B) Central nervous system problems, including psychosis with hallucinations, excessive brain stimulation (convulsions), drowsiness, confusion, insomnia, agitation, anxiety, irritability, nervousness, dysphoria, impaired cognitive test performance, dyskinesia, depression, and zombie-like constriction of affect and spontaneity;

(C) Gastrointestinal problems, including anorexia, nausea, vomiting, stomach ailments, dry mouth, and constipation;

(D) Pituitary dysfunction, including growth hormone and prolactin disruption, weight loss, growth suppression, growth retardation, anemia, exfoliate dermatitis, leukopenia, etc.

v. Misrepresenting to the consuming public, physicians and other interested parties, the efficacy of the drug Ritalin, without ever advising such persons that Ritalin usage would not stimulate or improve academic performance and/or have any long term effect on the symptoms associated with ADD and/or ADHD.

vi. Facilitating the creation of a new diagnoses in the DSM.

(b) Despite information in the medical and scientific literature concerning these side effects of Ritalin use, Defendants failed in all respects to advise potential consumers, doctors, and/or schools, teachers or other interested parties of the nature and extent of such side effects. Furthermore, Defendant CHADD similarly failed to provide adequate information to interested parties concerning the nature and extent of potential side effects.

36. Typicality of Claims. Plaintiff's claims are typical of the claims of Members of the Class, all of whom have purchased and/or ingested the Ritalin manufactured, distributed, and marketed by Defendants. Plaintiff and all Class Members have sustained, and will continue to sustain damages, injuries and irreparable harm arising out of Defendants' common course of conduct.

37. Adequacy of Representation. Plaintiff, by Deborah Voss, his Guardian ad Litem, will fairly and adequately protect the interest of Members of the Plaintiff Class. Plaintiff resides in California and purchased and/or ingested Defendants' products in California during the Class period.

Plaintiff is representative Members of the Class, are united by a common interest, and are adequate representatives since they have no interests that are adverse to the interests of absent Class Members. Plaintiff has retained counsel who are both competent and experienced in the prosecution of complex consumer fraud, mass tort and class actions. Plaintiff and his counsel intend to prosecute this action vigorously for the benefit of the Class. Plaintiff and his counsel will fairly and adequately protect the interests of the Members of the Class.

38. Superiority and Substantial Benefit. A class action is superior to other available methods for the fair and efficient adjudication of this litigation since individual litigation of Class Members' claims is impractical. Even if all Class Members could afford individual litigation, the court system could not. It would be unduly burdensome for the courts to adjudicate identical legal and factual issues in hundreds of thousands of cases. Individual litigation increases delay and expense to all parties, and especially the court system, associated with the resolution of the complex legal and factual issues of the case. The prosecution of separate actions by the individual Members of the Class would create a risk of inconsistent adjudications with respect to individual Class Members, thus establishing incompatible standards of conduct for Defendants. The prosecution of separate actions would create a risk of adjudications that would be dispositive of the interests of the other Class Members who are not parties to such adjudications, thus substantially impairing the ability of such non-party Class Members to protect their interests. Individual litigation of this case presents a great potential for inconsistent or contradictory judgments.

39. Class action treatment is a superior method of adjudication and provides a substantial benefit to the litigants and the courts since it presents far fewer management difficulties and provides the benefits of a single adjudication and comprehensive supervision by a single court. Furthermore, as the damages suffered by each individual Member of the Class may be relatively small, the expenses and burden of individual litigation would make it difficult or impossible for individual Members of the Class to redress the wrongs done to them. An important public interest will be served by addressing the matter as a class action. Notice of the pendency and of any resolution of this class action can be provided to Class Members by publication and broadcast.

40. Furthermore, Plaintiff's claims are certifiable as a Class action because Defendants

have acted or refused to act on grounds generally applicable to the Class, thereby making appropriate final injunctive relief or corresponding declaratory relief with respect to the Class as a whole.

41. Plaintiff, by Deborah Vess, his Guardian ad Litem, is unaware of any difficulties that are likely to be encountered in the management of this action that would preclude its maintenance as a class action. Accordingly, the proposed Class fulfills the certification criteria of California law and certification of the above-defined Class is appropriate under one or more of the provisions of California law.

FIRST CAUSE OF ACTION

CLASS ACTION FOR VIOLATION OF THE CONSUMER LEGAL REMEDIES ACT
[California Civil Code §1750, et seq.]
(By All Plaintiffs Against All Defendants)

42. Plaintiff hereby incorporates by reference the allegations contained in the preceding paragraphs as though fully set forth herein.

43. California Civil Code §1770 provides, in relevant part:

> The following unfair methods of competition and unfair or deceptive acts or practices undertaken by any person in a transaction intended to result or which results in the sale or lease of goods or services to any consumer are unlawful: . . .
>
> (2) Misrepresenting the source, sponsorship, approval or certification of goods or services;
>
> (3) Misrepresenting the affiliation, connection or association with, or certification by, another;
>
> . . .
>
> (5) Representing that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits or quantities which they do not have or that a person has a sponsorship, approval, status, affiliation, or connection which he or she does not have.
>
> . . .
>
> (7) Representing that goods or services are of a particular

standard, quality, or grade, or that goods are of a particular style or model, if they are of another.

44. Defendants have committed, and continue to commit, an unlawful method of competition, and unfair and deceptive acts in violation of Civil Code § 1770 by their commission of deceptive acts which have deceived and continue to deceive the consuming public, including Plaintiff. In particular, Defendants affirmatively misrepresented material facts and failed to disclose material facts to the Plaintiff, including but not limited to the following:

a. Actively promoting and supporting the concept that a significant percentage of children suffer from a "disease" which required narcotic treatment/ therapy;

b. Actively promoting Ritalin as the "drug of choice" to treat children diagnosed with ADD and ADHD;

c. Distributing misleading sales and promotional literature to parents, schools and other interested persons in a successful effort to further increase the number of diagnoses and the number of persons prescribed Ritalin;

d. Deliberately neglecting to address or provide adequate information to consumers, doctors, and/or schools concerning the many significant hazards of methylphenidate use and prescription, including, but not limited to, the following:

i. Cardiovascular problems, including palpitations, tachycardia, hypertension, arrhythmias, chest pain and cardiac arrest;

ii. Central nervous system problems, including psychosis with hallucinations, excessive brain stimulation (convulsions), drowsiness, confusion, insomnia, agitation, anxiety, irritability, nervousness, dysphoria, impaired cognitive test performance, dyskinesia, depression, and zombie-like constriction of affect and spontaneity;

iii. Gastrointestinal problems, including anorexia, nausea, vomiting, stomach ailments, dry mouth, and constipation;

iv. Pituitary dysfunction, including growth hormone and prolactin

disruption, weight loss, growth suppression, growth retardation, anemia, exfoliate dermatitis, leukopenia, etc.

e. Misrepresenting to the consuming public, physicians and other interested parties, the efficacy of the drug Ritalin, without ever advising such persons that Ritalin usage would not stimulate or improve academic performance and/or have any long term effect on the symptoms associated with ADD and/or ADHD.

f. Facilitating the creation of a new diagnoses in the DSM.

45. Plaintiff, pursuant to California Civil Code §1780, seeks an order of this court enjoining such methods, acts and practices and an order requiring the Defendants to undertake the following:

a. Disgorge all revenues and profits acquired as a result of the unlawful methods, acts and practices;

b. Provide restitution resulting from the unlawful method, acts and practices of defendants;

c. Pay exemplary damages; and

d. Any other relief this Court deems proper.

SECOND CAUSE OF ACTION

UNFAIR COMPETITION UNDER CALIFORNIA BUSINESS AND PROFESSIONS CODE SECTION 17200 (Against All Named Defendants)

46. Plaintiff hereby incorporates by reference the allegations contained in the preceding paragraphs as though fully set forth herein.

47. Plaintiff hereby brings this action individually and on behalf of the general public pursuant to Section 17200 et seq. of the Business and Professions Code of the State of California, the "Unfair Competition Act."

48. The acts complained of in each of the preceding paragraphs of this complaint, and each of them, constitute unfair and/or unlawful acts in competition in violation of Section 17200 of the California Business and Professions Code. Such acts and violations have not abated and will continue to occur unless enjoined.

to the APA's assistance, support, aid and collusion with Ciba/Novartis in creating a novel medical "diagnosis" that could be, and ultimately was, applied to a large percentage of children in the United States, and for which the APA, in combination with other defendants, continued and presently continue to promote the prescription, use, and sale of Ritalin.

23. Defendant CHADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder) is an unincorporated association dedicated and promoted to the principle that significant numbers of persons suffer from a "disease" that did not exist until 1980. CHADD works closely with Ciba/Novartis and the American Psychiatric Association.

24. Based on information and belief, CHADD has been a recipient of financial donations and contributions from Defendants Ciba/Novartis for many years. CHADD received $748,000 from Ciba/Novartis in the period 1991 to 1994 alone. During the periods when CHADD received funding from Ciba/Novartis, CHADD deliberately made efforts to increase the sales of Ritalin, and to increase the supply of methylphenidate available in the United States, and to reduce or eliminate laws and restrictions concerning the use of Ritalin and methylphenidate in the United States, all at the request, and to the financial benefit, of Ciba/Novartis.

25. Ciba/Novartis made such financial contributions with the purpose of advertising and promoting sales of Ritalin - an internationally controlled substance. Ciba/Novartis has thus repeatedly violated Article 10 of the United Nations Convention on Psychotropic Substances, 1019 U.N.T.S. 175 (1971).

26. CHADD's activities nationwide have led to a significant increase in the amount of Ritalin taken by school children and have directly resulted in enormous profits to Ciba/Novartis. In so doing, CHADD has promoted the concept of a diagnosis of "disease" or "brain damage" as well as promoting and supporting the concept that appropriate therapy for such a diagnosis is a prescription for Ritalin. In so doing, CHADD has acted as an agent of, and/or has aided and abetted Ciba/Novartis in its efforts to increase sales and earn additional profits from the sale of Ritalin.

CO-CONSPIRATORS

27. Each Defendant is sued individually as a primary violator and as a co-conspirator. The liability of each Defendant arises from each Defendant's agreement to commit unlawful acts and the

49. These violations have injured Plaintiff, the General Public, and fair and lawful competition. These violations have coextensively unjustly enriched the defendants. Plaintiff and the general public are entitled to injunctive, disgorgement/restitution, and other equitable relief.

THIRD CAUSE OF ACTION

INDUCEMENT THROUGH FALSE AND MISLEADING STATEMENT UNDER BUSINESS AND PROFESSIONS CODE SECTION 17500 (Against All Defendants)

50. Plaintiff hereby incorporates by reference the allegations contained in the preceding paragraphs as though fully set forth herein.

51. Plaintiff hereby brings this action individually and on behalf of the general public pursuant to Section 17500 et seq. of the Business and Professions Code of the State of California, the "Unfair Competition Act."

52. Notwithstanding their knowledge of the increased threat cardiovascular problems, central nervous system problems, gastrointestinal problems, and pituitary dysfunction, among other adverse consequences connected to the use of Ritalin, as described above, defendants, and each of them, continued to market, advertise and sell Ritalin to physicians, health care personnel and teachers, and to the General Public.

53. The acts of untrue and misleading advertising by defendants, and each of them, as described above presents a continuing threat to members of the general public of California in that their prescription and use of the drug methylphenidate presents the serious threat of hazards such as cardiovascular, central nervous system and gastrointestinal problems, as well as pituitary dysfunction.

54. The general public of the state of California have no other adequate remedy of law in that individual lawsuits would prove too time consuming and burdensome and would not properly address the monetary damage and equitable relief requested herein.

55. As a direct and proximate result of the aforementioned acts, Defendants received and continue to receive in excess of a billion dollars in sales from the sale of Ritalin to members of the General Public of California who were prescribed and ingested Ritalin, to their detriment.

56. These violations have injured the General Public and fair and lawful competition. These violations have coextensively unjustly enriched defendants, and each of them. The General

Public is entitled to disgorgement of profits, restitution and other equitable relief.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for relief and judgment against Defendants, jointly and severally, as follows:

For the First Cause of Action:

1. Plaintiff prays for injunctive and declaratory relief as a result of Defendants' violation of California Civil Code §1750 *et seq*, as follows:

(a) Injunctive relief to halt unlawful methods, acts and practices engaged in by defendants;

(b) Requiring Defendants to disgorge all revenues and profits acquired as a result of their unlawful methods, acts and practices;

(c) Requiring Defendants to provide restitution resulting from unlawful methods, acts and practices of defendants;

(d) Requiring Defendants to pay exemplary damages; and

(e) Any further relief this Court deems proper;

For the Second and Third Causes of Action:

1. Plaintiff prays for equitable relief for violations of Section 17200 and Section 17500 of the Business and Professions Code as hereinabove alleged. Such relief includes:

(a) Injunctive relief to halt prior violations of law and to assure fair and lawful competition, including court orders regulating advertising, marketing, and production practices;

(b) Restitution to plaintiff and the general public who have been injured or otherwise disadvantaged by defendants' unfair and unlawful acts in competition;

(c) Restitution sufficient to fully disgorge the revenues obtained from plaintiff and the general public for unfair and unlawful acts in competition;

(d) For attorneys' fees as provided by statute and/or pursuant to the "common fund" doctrine and/or pursuant to equitable principles of contribution.

For All Causes of Action:

1. For Plaintiff's reasonable attorneys' fees and costs.

2. For prejudgment interest as provided by law.

3. For costs of suit incurred herein.

4. For such other and further relief as this Court deems equitable, just and proper.

JURY DEMAND

Plaintiff herein demands a trial by jury.

DATED: September 13, 2000

DOUGHERTY, HILDRE, DUDEK & HAKLAR

By: _____

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HEADLINE: Psychotropic Drug Use Pushed On Children: Parents Duped By Experts

BYLINE: Oakwood, Dakota

BODY:

PSYCHOTROPIC DRUG USE PUSHED ON CHILDREN: PARENTS DUPED BY EXPERTS

BY DAKOTA OAKWOOD

THE HOMELESS, CRIMINALS, ELDERLY, drug addicts and mentally handicapped have all become targets for psychiatry's and psychology's **marketing** efforts -- providing of course, that government health care or private health insurance is footing the bill.

The most contemptible mental health strategy to date involves children. Recent history has shown that the defenseless innocence of children has failed to soften psychiatry's or psychology's quest for profit, and failed completely to inspire them to reassess the validity, safety, effectiveness or consequences of their drugs and treatments on children. Rather, it has sent them into a feeding frenzy. Children have been manipulated, used, deceived, sexually and physically abused, drugged, and killed -- all just business as usual.

Diagnosing Kids for Profit

The United States National Center for Health Statistics reported that between 1980 and 1987, the number of children between the ages of 10 and 19 who were committed to psychiatric units ballooned by 43% and today, that number is well over 300,000.

The main tool used to achieve this phenomenal growth rate was the DSM. The 1980 edition of DSM-III added 32 "mental disorders" to its "Infancy, Childhood, and Adolescence" section. Seven years later, in 1987, the handbook was revised, adding a further 29 disorders, including a dramatic increase in the section, "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence."

This ushered in a population of children with behavior problems that had never before been considered serious enough to require medical intervention, let alone hospitalization. The behavior and the kids were the kind that would formerly have been dealt with at home, by parents, as part of the normal tribulations of child-raising.

In 1987, the APA included "Attention Deficit Hyperactivity Disorder" (ADHD) in DSM-III-R. Within a year, 500,000 children in the United States alone were diagnosed with this bogus affliction. (www.dct.com/tlavaque/**ritalin.**html)

This was further fueled by federal government incentives in 1990, when low-income parents whose children were diagnosed with ADHD were given more than $450 a month. In 1991, federal education grants also provided schools with $400 in annual grant money for each child diagnosed with ADHD. The number of children diagnosed with this "disorder" soared again. By 1997, the number of children labeled as having ADHD had risen alarmingly to 4.4 million.

What this mostly boils down to is the lack of good medical practice and the drugging of entirely normal children all in the name of money. Charlie was a 10-year-old who suffered mood swings, yelled obscenities, kicked his sister, couldn't control his temper, argued with his teachers and had low grades. He was suspected of having "attention deficit disorder" or "conduct disorder" but was eventually labeled as "hyperactive." His mother was told, "You have two choices: give him **Ritalin,** or let him suffer." Charlie was put on **Ritalin,** but a second medical opinion -- based on physical examination and thorough testing -- discovered he had high blood sugar and low insulin. Either condition, if uncontrolled, can lead to mood swings, erratic behavior, and outbursts -- the very symptoms hyperactive Charlie exhibited. After proper medical treatment, Charlie was fine and his grades in school went up.

Several doctors have researched this "ADD (ADHD)" and it has not been proven to be a disease, or anything physical or biological. ADHD was announced in 1998 as a fraud intended to justify starting these children on a life of drug addiction and manipulation. It was felt that most of these children needed to be tested for allergies. It is malpractice to remain ignorant of the nature of the "hyperactive child disorder" and ignorant to advise drug treatment which is unscientific and wholly harmful.

The diagnoses of ADD is entirely subjective and is interpretation. Maybe a child blurts out in class or doesn't sit still. The lines between an ADD sufferer and a healthy exuberant kid can be very blurred.

However, business as usual means that millions of normal children continue to be prescribed dangerous, mind-altering drugs all over the world. One of the main drugs, **Ritalin,** is an amphetamine-like drug which is potentially addictive, can cause symptoms ranging from thought disorder to insomnia and cardiac arrhythmia, and can stunt a child's growth. Suicide is a major complication of withdrawal from this and similar drugs. **Ritalin** has been called "Kiddy cocaine" because of its effects on the brain and because it can lead to cocaine or other illicit drug usage.

Business as usual also means that the number of children placed on psychotropic drugs has escalated out of control: six million American children are prescribed these drugs including 909,000 who take Selective Serotonin Re-uptake Inhibitor (SRRI) antidepressants.

Psychiatry & Psychology in Our Schools Destroy "Right & Wrong"

It has been studied and discovered that feelings, personal growth, and totally non-judgmental attitude are emphasized in programs in school where no models of good behavior are provided. There are no reasons given why a boy or girl should want to be good in the first place. They come away with the impression that even the most basic values are matters of dispute. This is why kids' scores are low and why morals are on a steep decline.

Under the guise of mental health and student assessment, consultants in the schools as psychologists are using government grant process for infusing experimental therapies, many of them medically dangerous and politically motivated into school testing programs and cirrcula.

In Pennsylvania, teachers used a 61-question psychological survey called the Disruptive Behaviors Disorders Rating Scale. Some of the questions were taken straight from DSM-IV. The information was

collected without the knowledge or consent of many parents, allowing teachers to rate each pupil on everything from fidgeting in class to "excessive" talking, humming, impulsiveness, forgetfulness, and bossiness. The data was computerized by Western Psychiatirc Institute and the parents had to go to court to force the Institute to destroy the potentially harmful and invasive information.

What do we have to show for our schools being turned into mental health clinics? Literacy levels have crashed and the very problems that psychiatrists and psychologists have been paid to prevent -- violent crime, drug abuse and child-teen suicide -- have spiraled out of control.

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HEADLINE: Increased Rx use by preschoolers troubles Senators; Brief Article

BYLINE: Conlan, Michael F.

BODY:

A report of increased off-label prescribing of psychotropic drugs to preschool children has provoked calls from two key lawmakers to make pediatric testing an even higher federal priority. "Forcing children to accept 'hand-me-down' medicines is dangerous and unacceptable," said Sen. Christopher Dodd (D, Conn.) .Sen. Mike DeWine (R, Ohio) added that parents "should not be forced to guess the proper safety, effectiveness, or dosing of pharmaceuticals for their children when those drugs are only labeled for adults."

The Senators, who drafted a 1997 provision that provides Rx makers with six extra months of patent protection and other incentives for undertaking pediatric testing, urged the Food & Drug Administration and the National Institutes of Health to make pediatric testing and research an even higher priority. They were responding to a study in the Feb. 23 Journal of the American Medical Association. The study found the use of stimulants, antidepressants, and neuroleptics, including **Ritalin** (methylphenidate HCl, Novartis) and Prozac (fluoxetine HCl, Lilly) in children aged two to four had doubled, and in some cases tripled, between 1991 and 1994.

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HEADLINE: Drug Rush; hazards associated with fast new drug approvals

BYLINE: POMPER, STEPHEN

BODY:

Why the prescription drug market is unsafe at high speeds

THE DRUG WORLD THAT AMERICANS once worried about was a shadowy demi-monde populated by hollow-eyed junkies toting needles, spoons, and Jefferson Airplane LPs. But times have changed, and a new drug culture requires our attention. The pushers in this culture wear lab coats and business suits and move their product through HMOs and family doctors. And although their drugs may be government regulated, that does not make them safe. According to statistics cited by Food and Drug Administration officials, toxic reactions to marketed drugs are estimated to cost more than $ 30 billion per year and be among the ten leading causes of death in the United States.

You might think that under the circumstances, the government would be pouring enormous resources into evaluating the hows and whys of prescription drug fatalities, but it is not. Industry-supported reforms have provided the FDA major resources to focus on the approval of new drugs, but once these drugs are out in the market, the picture changes dramatically. The group that keeps track of whether these drugs are hurting the people who are taking them is one of the agency's weakest stepchildren. It has limited clout within the FDA. It scrapes by on between $ 10 and $ 15 million a year--less than what Eli Lilly was estimated to spend on its 1997 Prozac ad campaign according to The New York Times. It relies on voluntary and unreliable reporting by doctors for most of its information. In the words of Carol Scheman, an FDA deputy commissioner in the 1990s, the nation's system for keeping track of the bad effects of prescription drugs is "appallingly bad."

That's particularly lousy news when you consider the speed at which new drugs are being approved and the remarkably aggressive, almost reckless, promotional efforts that go into making them sell. Consider that six new drugs approved since mid-1996 have been pulled off the market, one of the most recent being the diabetes drug Rezulin. Larry Sasich of Public Citizen's Health Research Group points out that all six of them were "me too" drugs: They treated symptoms that were already treatable with existing medications. Nevertheless, millions of prescriptions were written, and more than 150 deaths were linked to these medicines before they were pulled off the market. And because reporting is unreliable, the actual body count could be up to 100 times greater.

Perhaps you're thinking fine, if the system is imperfect, at least doctors are protecting their patients from

unsafe new drugs. But drug companies may push doctors to prescribe their drugs even when they're reported to be unsafe. Rezulin is a case in point. In January 1997, the FDA approved Rezulin under its accelerated "fast track" procedures following six months of testing. But it wasn't long before users started dying, the United Kingdom's Medicines Control Agency revoked its approval, and FDA insiders started working with the media--notably David Willman of the Los Angeles Times--to get the word out that Rezulin was just not safe.(*) In March 1999, with the death toll approaching 30, senior FDA epidemiologist David J. Graham publicly told an FDA advisory board that every single patient taking Rezulin was at risk of sudden liver failure. Given all this, and given that there were drugs on the market that treated the same type of diabetes as Rezulin and did not fry a patient's liver, why would a doctor still prescribe Rezulin?

You'd hate to think the answer could be: "Knicks tickets." In a fax that went out to select New York area physicians in spring 1999, Rezulin's manufacturer, Parke-Davis (a Warner Lambert subsidiary) invited guests to attend a "special scientific lecture" at "the Club Bar and Grille ... Madison Square Garden." After a short lecture and Q & A over dinner, the guests would be ushered down to their seats in the stadium where they would watch a "BASKETBALL GAME!!!! New York Knicks vs. Toronto Raptors." Perhaps you're thinking that it takes a certain amount of chutzpah to throw what is effectively a basketball party for a product that is widely suspected of killing people, but chutzpah is often what good business is all about.

The problem is, it's not always consistent with good medicine.

Maginot Line

As the nation's drug regulator, the Food and Drug Administration should be the first line of defense against drug companies that are pushing dangerous product. But asking the FDA to rein in the pharmaceuticals industry is a bit like sending someone out to catch Niagara Falls in a bucket. The industry has vastly greater resources to press its agenda. And changes in drug laws and regulations have encouraged a boom market for drugs that the agency is not equipped to police.

To get a feel for the mismatch in financial resources, consider the following: The FDAs annual budget for approving, labeling, and monitoring drugs is roughly $ 290 million. To that figure, add the $ 2 or $ 3 million available to Public Citizen's Health Research Group, which was formed to help even the balance between regulators and the drug industry. Now compare those numbers to the $ 11 billion promotional budget that the drug industry gives itself according to a recent article in the Journal of the American Medical Association.

In order to get a full picture of what the FDA is up against, however, you have to step back and see how dramatically the regulatory landscape has changed in the last decade. Back in the early 1990s, there was a widely shared perception that the FDA was too slow to approve new drugs even when they might offer desperately needed help for people who were dying. AIDS activists were particularly eager to light a fire under the approvals process out of concern that the FDA might be holding up life-saving or life-prolonging treatments. They were well connected and highly committed, and they had the support of an industry that wanted faster approvals for its own reasons. It therefore was no great surprise that in 1992 Congress passed a new law creating the blueprint for a faster approvals process. Under the new law, the FDA would hire more reviewers and take the other steps necessary to speed up reviews without sacrificing rigor, and industry would bear the additional costs by paying "user fees" with every new drug application.

But if AIDS helped to crack open the door for faster drug reviews, the pharmaceutical industry was standing right there to kick it wide open. The new law created a faster review process for all drugs--not just breakthrough treatments for diseases like AIDS. This meant that as approval times have dropped from 30

to 12 months on average, there has been a rush of newly approved drugs which do not offer the public any new treatment benefits, but which could pose new risks.

And to compound the impact of the newly-approved drugs, in 1997 the FDA yielded to years of industry pressure and loosened restrictions on consumer advertising. This made it possible for drug companies to advertise on television without spending huge chunks of time describing risks and side effects. Ads for new drugs like Viagra and Claritin became almost as familiar as Burger King commercials. New products generated blockbuster sales in a matter of months.

But while the changes have been a hit commercially, they have created some major problems in the FDA. Probably the biggest is that the changes do no permit the FDA to spend a single dollar of the industry fees it collects to track whether all those new drugs are safe once they hit the market. As a result, the FDA is in approval overdrive, while its safety side is stuck in low gear: The parts of the agency that review and approve new drugs (call them the "review teams") have around 1,300 employees helping process new drug applications. By contrast, the part that tracks whether new drugs are hurting people (call it the "safety team") has 72 employees, including only 13 with formal training in epidemiology--the science of spotting medical disasters.

Former FDA commissioner Donald Kennedy says that the FDA's system for keeping tabs on how and when drugs hurt people is "terrible." "We don't know enough to know when drug problems arise," he says. "And when we know enough, it takes a lot to get them off the market." Part of the problem is that in today's overheating promotional environment, new drugs are likely to generate huge sales more quickly than ever, and therefore may create more damage in a shorter amount of time. Unfortunately, the FDA's safety team relies on tools that were designed at a time when speed wasn't so important. Instead of looking for information, it waits for bad news to come in from doctors (who are not required to report bad drug reactions and therefore only do so sporadically) and drug companies (who are required to report adverse events but get most of their information from doctors). The system is ad hoc at best: Estimates are that only between one and 10 percent of adverse drug events get reported.

Moreover, even when the safety team identifies a problem drug, it has limited authority to act. It evaluates a drug's riskiness and makes a recommendation about what the agency should do. But according to the head of the team, Dr. Peter Honig, it plays a "consulting" role. The review team that approved the drug in the first place analyzes its benefits, communicates with the manufacturer, and seems to have the upper hand in helping agency higher ups decide whether or not to withdraw it. Critics rightly argue that the safety team should be given more deference, first, because the review team that approved a drug may not be objective about whether to withdraw it and, second, because the rest of the agency lacks the epidemiological training that is crucial in order to "get" the risk analyses that the safety team produces.

But given that for now the safety team is low man on the FDA totem pole, can the regulators with more clout be relied on to keep the drug companies in line? It's hard to respond with a confident yes. Although the agency's review teams have a whistleblower tradition that dates back to Frances O. Kelsey (the heroine who blocked thalidomide from the U.S. market), a review officer who objected to Rezulin's initial approval was taken off the case and a reviewer-turned-whistleblower during the Rezulin affair became the object of an internal affairs investigation. Drug company reps tend to hover over the agency's approvals process and, according to a recent in-house newsletter, may resort to tactics from name-calling to going over a reviewer's head if problems arise. And in the wake of the Rezulin matter it has been suggested that management--particularly Commissioner Jane Henney and her drug deputies Janet Woodcock and Murray Lumpkin--may identify too strongly with industry.

Is that fair? Consumer advocates like Larry Sasich of Public Citizen argue that Henney "sold the farm" to

get confirmed by a Republican Congress, and that the agency has been "completely coopted by industry." But defenders insist that management's mistakes are more innocent: They reflect the sort of runnel vision that commonly afflicts bureaucrats who stake out positions and then can't admit to getting them wrong. And former colleagues like ex-Deputy Commissioner Carol Scheman bristle at the suggestion that Henney's team yields to industry pressure. "I don't think it's possible," she says. "These are among the most rigidly moral people I know."

A deliberate sell-out by FDA management is highly unlikely. But it is more probable that there is an unconscious tendency to hear the loudest voice. And in the context where they operate, that voice belongs to the drug industry. After all, the new drug laws have enhanced the industry's role in the drug approval process. And every year FDA management has to seek appropriations from an anti-regulatory Republican Congress with many friends in the drug business. Under the circumstances it's not hard to imagine how a person could find herself listening just a bit harder to the drug companies.

Given that the FDA's safety team is anemic, reviewers feel like they're being hassled, and management is whipsawed between science, politics, and industry, doctors are an increasingly important buffer between potentially dangerous drugs and the public. But if the basketball promotion that Parke-Davis put on for Rezulin is any indication, the drug industry is intent on wearing them down. And Knicks tickets are just the tip of the iceberg.

Tricks of the Trade

Finding a doctor who will confess outright to being influenced by pharmaceutical company promotions is a thankless proposition. But the general absence of Hippocratic self-awareness cannot change the facts. As noted above, the pharmaceutical industry spends $ 11 or $ 12 billion a year and a lot of brain power figuring out how to push doctors' buttons. You don't part with that kind of money unless you get some kind of return on your investment. And to put a finer point on it, a study published this January in the Journal of the American Medical Association (entitled, appropriately enough, "Is a Gift Ever Just a Gift?") concluded that the various tools in the drug company sales kit do in fact influence doctors' prescription practices and in some cases lead to "non-rational" prescribing.

The basic form of promotion is the sales call. Drug companies spend $ 5 billion a year sending representatives--called "detailmen"--to doctors' offices. While the companies argue that detailing provides a valuable educational service by keeping physicians up-to-date on the latest changes in medical science, detailing (like any sales call) is more manipulation than education. Sales reps keep FBI-style dossiers on physicians that include info from the names of family members to golf handicaps to clothing preferences. A national service called IMS Health gives them database printouts on exactly what prescriptions the doctor has been writing. And detailmen are under intense competitive pressure to do what it takes to make a sale. Pharmaceutical Representative--a trade journal--features columns with sales tips on everything from how to handle a doctor who says that your product caused a terrible allergic reaction ("You might say 'Wow! There's only a 0.01% chance of that happening'") to tricks for gaining access ("You must find ways to 'get in the physician's face'") to the more banal secrets of throwing a successful sales dinner ("Arrange in advance to cover valet parking and tips").

Which brings us to the subject of bribes--otherwise known as "gifts," "samples," and "entertainment." It's true that drug representatives have toned down their peddling techniques a bit since 1990, when the FDA passed regulations forbidding "gifts of substantial value." But what those regulations really seem to have accomplished has been to shift the emphasis from expensive hardware like stereos and fax machines to promotional trinkets and meals and travel. "Doctors are still going to dinners and on cruises and to baseball games," says Dr. Bob Goodman, an internist at Columbia Presbyterian Hospital in New York who also

runs "nofreelunch.org," a Web site dedicated to the eradication of medical graft.

Of course you can't just offer a self-respecting professional a bribe. One of the key arts in pharmaceutical salesmanship is to convince the doctor that he somehow deserves what he's getting. Dr. Jerry Avorn, a professor at Harvard Medical School, says that salesmen often couch their dinner invitations in flattering terms like "Come on--you're a busy guy and you've gotta eat anyway; I'll just pick up the tab." And to cover docs who'd rather eat with their families, Dr. John Mohrer says that detailmen in Queens, New York have inaugurated a tradition called "Dash-'n-Dine." It involves going for Chinese takeout and sitting with a detailman and maybe an invited guest while your order is being prepared. "You go in and schmooze with them, they buy you a drink, and they tell the cook to take it slow," says Mohrer. "The last time I was there they'd brought in an endocrinologist from 75 miles away to talk about Rezulin." After a half an hour or so of light, boozy sales patter, the cook produces the order, the detailman produces his wallet, and the doctor walks away with dinner for the whole family.

If the doctor is just a stick in the mud, then making inroads with the staff is another option. Abbey Meyers of New Fairfield, Connecticut recently emerged from an appointment with her arthritis doctor to find a detailwoman stocking the sample cabinet and chatting up the receptionist. "Say, how about I come by next week and take the staff to lunch," asked the detailwoman. What about the doctors? "We'll just bring them back takeout" came the reply. Meyers, who is attuned to these things as president of the National Association for Rare Disorders, notes that the advantages in targeting the rank and file are clear enough: Nurses and physician assistants have doctors' ears and keys to the sample closets that reps like to stock with their wares.

Of course samples aren't quite the freebies that they seem. Although some are used for indigent patients, they're more generally used like baited hooks. The patient who goes home with a pocket full of free medicine from his doctor may feel like he's making out, but he's really forming a debt of gratitude toward his doctor, who in turn feels gratitude toward the drug company. It's easy to see how through all this warm feeling a doctor can become more inclined to prescribe the medicine and the patient can be more inclined to ask for it.

Of course one of the easiest and most common gambits that sales reps use is to stock an office larder with small toys of insubstantial value that have the Manchurian Candidate effect of pricking a doctor's subconscious when it's prescription writing time. These paraphernalia--pens, pads, small toys with the company's logo--are by design too small to provoke suspicion and yet can be deviously effective. "I did a study at North Shore 10 years ago," wrote Dr. B. Robert Meyer in a recent email to the nofreelunch web site. "Drug lunch with pizza by the piperacillin rep. Gave out 'pipramints' to the house staff and some info about their drug ... Our piperacillin use went from $ 5,000 to $ 15,000 in the next month."

But Meyer thinks that the doctors are to blame more than the detailmen for the graft element in pharmaceutical sales. He wrote to nofreelunch: "If you talk to the representatives and get them to let down their hair about things, they will tell you horrifying stories of out-right extortion by physicians, as in 'I won't prescribe any more of your product unless you get me good seats to the Yankee game next Saturday. I used to think that these were few and far between, but the more reps I talk to, the more stories I hear.'" Other doctors confirmed that hold-ups of this nature are altogether too common. "Many of us are for sale," concludes Meyer. "And therein lies the problem."

Pull Out All The Stops

To the extent Dr. Meyer is right, Yankee tickets may be the least of it. People both in and outside the pharmaceutical industry told me that if you really want to buy a doctor's loyalty, then you need to get her

on the company payroll. "Get them on the payroll and it's amazing the prescribing they will do," one pharmaceutical company insider told me. But how do you get them there?

One way is to take a page out of Searle Pharmaceuticals' book. When Searle wanted to promote its new drug Celebrex, it invited 300 doctors and pharmacists to Orlando, Florida for a winter weekend getaway. According to Thomas J. Moore, who wrote about the episode in Washingtonian magazine, Searle had used IMS data and other sales rep info to pinpoint these particular individuals as opinion leaders who would be useful spreading the Celebrex gospel in their communities. The purpose of the Orlando weekend was therefore to recruit them to a national "speakers bureau" for the new drug. For their trouble, Searle paid the doctors $ 500 for coming to Florida and $ 500 for each speech on Celebrex they gave after becoming a member of the team. Plus, the company pulled out all the stops in Orlando.

"It was truly disgusting the money they spent," said one participant to Moore. "Shrimp the size of your finger. Would you like the filet mignon or the salmon? Open bar all the time. It wasn't just scotch--it was Chivas Regal." In addition, Searle was thoughtful enough to rent out Universal Studios theme park for an evening, and far-sighted enough to have attendants standing by with umbrellas when a cloudburst threatened to ruin the fun.

Of course it's hard to say how much the three hundred Orlando conventioneers contributed to the success of Celebrex, but it's worth noting that the drug generated roughly a billion dollars in sales during its first year on the market the first drug ever to attain that mark in its first year out. And what great breakthrough did Celebrex offer to merit these results? Actually, it's a painkiller--like aspirin, acetaminophen, and ibuprofen, but with a slightly different chemical action. Moore notes one other difference too: In some of the tests performed for FDA approval, Celebrex actually turned out to be less effective than painkillers already on the market.

Prescription for Disaster

Some doctors argue that detailing gimmicks and promotional trips are just advertising and can be discounted as such by a discriminating professional. If you buy that (and the studies suggest you shouldn't), then there are still other forms of promotion to be concerned about. One of the most pernicious is industry-funded research and training.

The funding game works like this: In one corner are academics, who need to get published and to get grants. In the other corner are companies, which like studies that make their products look good. And in the background, as Eyal Press and Jennifer Washburn recently described in The Atlantic Monthly, is the fact that industry funding for academic research octupled between 1980 and 1997, as research costs climbed, and the rate of growth of federal support declined. So it's not a great surprise that researchers often look to companies for grants, and companies often look to researchers for studies that will make their products look good.

How do they know that these studies will in fact make their products look good? They just do. In the first place it turns out that even when sponsors aren't involved, the great majority of drug studies shed favorable light on the products being examined. In a 1996 study in the Annals of Internal Medicine, Stanford University's Mildred Cho found that on average 79 percent of papers on unsponsored research reflected favorably on the drug in question. While that's a pretty impressive number, it's almost modest compared to Cho's finding that the percentage went up to 98 percent for papers on industry-sponsored research. (This doesn't seem to bother most medical journals, which will publish sponsored research so long as the conflict has been disclosed; the New England Journal of Medicine has a rule that it won't publish sponsored research at all, but in February it admitted to breaking it 19 times in the past three years.)

Why are researchers so favorably disposed to the drugs they're peering at? Perhaps they've had friends who learned that coming forward with negative results can land you in a heap of trouble. Indeed, some researchers who have tried to publish unflattering findings have been threatened with lawsuits. In one troubling case from the mid-'90s, a U.K. drug company called Boots threatened legal action against University of California researcher Betty Dong in order to keep her from publishing a study that they had funded on one of their products. The study showed three Boots competitors to have products just as good--which apparently was not the finding the company had been hoping for. Dong eventually got the right to publish, but by that time, Boots had assembled another research team that reached the opposite conclusion and published it elsewhere.

By contrast, if you publish a couple of papers that a drug company likes, they may decide to put you on the symposium circuit. Dr. Michael Gorback recalls that several years ago, when he was on the faculty of Duke Medical School, Smith Kline asked him to do a presentation on an antacid they were **marketing** called Tagamet. According to Gorback, for the occasion the manufacturer "pulled together a panel of myself, a Harvard med school professor, and a chairman from one of the University of California medical schools."

Gorback says he was flattered by the invitation until one day he went to the mailbox and found that Smith Kline had sent him an entire precooked presentation, complete with lecture script and slides. He says he complained to the company that he had his own ideas but quickly learned he was swimming against the tide when the company flew him up to Boston for a pre-meeting that ended up more like a rehearsal. According to Gorback, they were just getting started when the Harvard professor come running in, late and out of breath, and shuffling the script; he announced that he hadn't gone through it yet, but that was O.K.--they should do a read-through to gauge the time.

Gorback was astonished. "This is a guy who trained me," he says. "He has an international reputation. And he was going to put his seal of approval on script without reading it." Moreover, symposium papers often travel further than the symposia where they're read. They may be reprinted in bound "supplements" to medical journals (which have the same livery and typeface as the journals themselves). These supplements can then be passed out by detailmen in the hopes that doc will ignore the small print making clear that this isn't exactly pure science.

When Gorback describes the Tagamet event as "one of the most disgusting experiences of my career" he's talking about the ethics on the dais. But he may have missed other, more earthy, forms of seaminess out in the crowd. In an earlier article in these pages, Alexander Kippen wrote about how a former Texas detailman named Jody Perez who sold for a Johnson & Johnson subsidiary would work a symposium crowd. ("Doctored Results," October 1990) First, he'd suck up to his targets by letting them win phony contests (like guessing the number of pills in a jar). Then, once he got close enough, "I'd find out what their hot button was." It might be booze; easy enough. It might be women; when on familiar turf, Perez kept a list of local nurses, secretaries, and receptionists who liked to entertain visiting doctors. And it might be, surprise, drugs. Some of Perez's customers had a real fondness for codeine-laced Tylenol IV (liquid formula), which Perez called "juice" and which the docs liked to put in their cocktails to give them an extra kick.

Overkill

If codeine won't do it, another way to get to doctors is through their patients. And that's why consumer advertising has become so important. Television advertising has exploded since 1997 when the FDA eased regulations. Drug companies spent $ 900 million on consumer ads in the first half of 1999 alone. What's

wrong with more ads? Primarily the fact that they're so effective.

If a television ad convinces you that you need (or simply want) a drug, there's a good chance you will be able to convince your doctor to prescribe it. A recent study published in Health Affairs magazine reported that three-quarters of the respondents saw a drug on TV and asked their doctors for it were successful. In part that's because most doctors won't argue with a patient's prescription preferences unless the medication is going to hurt him. In part it's because they don't have time to argue: In today's HMO-driven world, appointments are so short that a doctor may give you the damn Viagra prescription just so that he can get your cooperation on whatever more important issue is at hand. And it may also be because your doctor sees the ads as a way to drum up business, and wants to encourage you to drop by whenever one captures your fancy.

This can't be a good development. In the first place, the most heavily promoted drugs are often the new ones, which the drug makers are hoping to turn into Celebrex-style blockbusters. These drugs may be FDA-approved--but the FDA only requires clinical testing in populations of about 3,000 people. If this turns out to be a drug that kills one in every 10,000 people, you probably only want to be one of the first 10,000 if you're pretty seriously afflicted and don't see many alternatives. Ten years ago when the FDA was more sluggish with the approvals and drugs tended to go on the market in Europe before here, you might have tried to find out whether 10,000 Germans had survived the experience. But now, 60 percent of new drugs come on the market in the U.S. first, making us the world's guinea pigs. And even if a new drug is safe, there's a more pedestrian consideration: It may not be any better than the invariably cheaper stuff that's been around for ages and gone generic.

In addition to consumer advertising, drug companies get through to consumers by sponsoring "patient groups" that consume whatever drug the company is pushing. For example, it was revealed several years ago that the non-profit group CHADD (Children and Adults with Attention Deficit Disorder), which offers encouraging information on using **Ritalin** and other psychotropic meds to control hyperactive kids, is partly funded by **Ritalin's** manufacturer--Novartis. It has also been reported that the Boots company, which manufactures a thyroid product, has at various times provided 60 percent of the funding for the American Thyroid Association. And the list goes on. What's irritating, if not outright dangerous, is that at least some patient groups wind up effectively advertising sponsors' products either by endorsing them directly or by lending credibility to the sometimes fuzzily defined syndromes (e.g., ADD) that the products "treat." Even people in the industry will concede off the record that groups acting as advertising agents for manufacturers should be subject to FDA regulation. But they're not.

Fix It

At the root of all of the problems in America's prescription drug culture is the fact that the pharmaceutical companies have seemingly bottomless resources to get their message out and the regulators don't have enough to ride herd. It's time to change that by finding new ways to put out objective information about drugs and rein in the misleading stuff that the drug companies release. But most importantly, we need to pour resources into developing a system that can actually detect bad drugs in the market before they become full-flown public health disasters. A few recommendations:

First, no more gifts or entertainment. It's time to tighten the rules again: If detailmen want to hand out reprints, fine. But there's no reason for them to be picking up meals, leaving pens and mints, and engaging in other forms of small-bore thought control that serve no redeeming medical purpose. And as for samples, these should only be permitted to the extent they're given out to the indigent or uninsured.

Second, increase federal funding for unbiased research. The more resources the government can provide,

the more balance there is likely to be in the scientific literature that doctors use to form their medical judgments.

Third, go back to the old rules for TV advertising and regulate patient group promotions. Television drug ads seem to be more capable of harm than good, so let's go back to the old system: Sponsors should have to recite a generous description of a drug's risks if they wish to advertise it on TV. Even if patients tune out this part of the ad, the weightiness of the description is helpful in conveying that this is a potentially dangerous product. This in turn would likely have a chilling effect on drug companies' inclinations to advertise on the small screen. As for patient groups that shill for sponsors--their promotional efforts should be regulated by the FDA as though they were agents for the manufacturer.

Fourth, organize "academic" detailing. Doctors need to get information from people other than salesmen and hired guns like Dr. Gorback and his co-panelists. A few years back, Harvard med school profs Jerry Avorn and Stephen Soumerai came up with a way to achieve this called "academic detailing" The basic idea is that medical schools would send their impartial detailers without any drug company ties to brief doctors on the latest drug advances. They found that doctors were more receptive and willing to spend time with detailers who had no economic interest in the treatments they were describing. How would the system work in real life? Soumerai says that Australia presents one possible model. There, the government organizes and funds detailing of this nature. Our government should do the same.

Finally, and most important, create a drug safety system that can effectively track what all of the drugs rushing on to the marketplace are doing to Americans' health. That the drug companies are allowed to fund a souped up approval process without putting some money into the FDA's safety team is troubling. That this safety team has to monitor the effects of more than 3,000 prescription drugs on 200 million people with a budget of around $ 15 million a year is just scary. It is an open secret in Congress and within the FDA that these resources are totally inadequate, so it's time to pony up. Congress should amend the user fee legislation to provide that more money goes to building a real safety system. If this means the review teams won't be able to meet their current targets for new drug approvals, they should put non-breakthrough drugs on a slower track: A number of reviewers would surely applaud this outcome. In the event that additional funds are required, Congress should appropriate them.

What would the safety system look like? It would be capable of collecting the information required to figure out how drugs are being used and whether they're causing harm, much as the Centers for Disease Control keep tabs on the spread of diseases. And it should play a much more substantial role in the process by which drugs are removed from the market. It should not be required to take a back seat to the original review team when it comes to deciding whether or not to pull a drug off the market. And some have suggested that it might even be formed outside the agency, in the same way the National Transportation Safety Board exists outside the Federal Aviation Administration, to give it some objective distance from the politics and matters of professional pride that impact decision-making.

Creating such a system, and taking the other four steps recommended above, could go a long way toward compensating for the wretched excesses of America's prescription drug culture. And who knows, they may lessen the chance that your doctor prescribes a drug that shouldn't be on the market for reasons that aren't quite rational--like the fact that the Knicks took the Raptors in overtime. Now, don't you feel better already?

(*) William also reported on Rezulin in the Monthly. ("Bitter Pill," September 1999)

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HEADLINE: Let's explore the 'why' of prescribing psychotropic medications to preschoolers.

BYLINE: Fritz, Gregory K.

BODY:

Advances in the development of medications to treat psychiatric disorders have accelerated in recent years. Fifty years ago no drugs were known to be effective for psychiatric illnesses such as depression or schizophrenia, and psychiatrists relied on such treatments as electric shock, insulin coma and wrapping with wet sheets to manage disturbed patients. Physicians now have dozens of medications to choose from, each with at least some demonstrated area of effectiveness and many with minimal apparent side effects. Even severe psychiatric illnesses are now eminently treatable, and hopes for the future are bright.

But amid the excitement and optimism, a recent study suggests that things may be moving too fast, particularly with regard to children. Julie Mango Zito, Ph.D., and Daniel J. Safer, M.D., and colleagues reported in the February 23 issue of the Journal of the American Medical Association that there has been a dramatic increase in the number of preschoolers taking psychoactive medications, especially stimulants and antidepressants. For example, the use of the most common stimulant medication in two- to four-year-olds increased an average of 260 percent across three sites between 1991 and 1995. With impetus starting at the White House, the National Institute of Health, a congressional committee and professional organizations rapidly are mounting investigations of medication prevalence in very young children.

Why has this report generated so much concern? What's wrong with many preschoolers taking medications if they're safe and helpful? At present, although most drugs have passed FDA testing on adults, the younger the patient population the less evidence there is for the safety, efficacy, proper dosage or long-term effects of a particular medication. Even **Ritalin,** the most thoroughly investigated psychotopic drug used in child hood, has not been approved for use in children under six years of age. Further, establishing a psychiatric diagnosis in a toddler or preschooler is difficult and time-consuming, and it's likely that many young children are being prescribed medications without an adequate evaluation. The rapidly developing brain of a young child is potentially susceptible to negative effects of medications that would not be a problem in the fully developed brain of an adult. Finally, prescribing a medication treatment if not accompanied by family and/or behavioral intervention may leave the main problems unaddressed.

Given the special risks and uncertainties associated with psychopharmacologic treatment in preschoolers, what factors might be behind the increased use of such drugs? One possibility is scientific enthusiasm. As

more is learned about the human genome, it's becoming clear that most psychiatric disorders have a significant genetic component and that the risk for adult disorder potentially is known early in childhood. However, environmental changes (either internal, physiologic or external, sociofamilial changes) can modify the expression of a gene, effectively changing the risk for adult disorder. This knowledge leads mental health professions toward earlier and earlier intervention, in the hope of preventing serious psychopathology later in life. Medications represent one available physiologic intervention.

Other, less admirable possibilities exist. In an era when financial concerns often dictate treatment, medication prescription requires less time than family counseling or behavioral therapy and, therefore, is cheaper, a fact not lost on those who pay for health care. Most psychiatrists have experienced managed care reviewers' not-so-subtle expectations that serious treatment involves medications. Although it's difficult to determine the impact of pharmaceutical advertising, the mil lions of **marketing** dollars focused on physicians may well influence their prescribing practices. Still another factor may be pressure from parents or teachers for a medical answer to young children's behavior problems that have complex roots. Whatever the reasons, we need to take a serious look at whether society's desire for quick, inexpensive solutions is coming at the cost of inappropriate medication use in preschoolers.

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PR NEWSWIRE

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HEADLINE: Adderall(R) More Effective than Methylphenidate at Reducing Symptoms of Attention Deficit/Hyperactivity Disorder

BODY:

- Benefits of Adderall Also Shown to Last Longer Than Those of Older ADHD Therapy -

SAN ANTONIO, May 15 /PRNewswire/ -- A new study published in this month's Journal of the American Academy of Child and Adolescent Psychiatry found that Adderall(R) (mixed salts of a single-entity amphetamine product) is significantly more effective at reducing inattention, oppositional behavior, and other symptoms of ADHD than methylphenidate, an older ADHD treatment. The study of 58 children with ADHD also found that the benefits of Adderall last longer than those of methylphenidate (which is sold under the brand name **Ritalin**(R)). In fact, 70 percent of patients taking a single morning dose of Adderall found significant improvement in ADHD symptoms, while just 15 percent of patients taking methylphenidate improved significantly with only one dose.

"In our study, children with ADHD showed more improvement after Adderall treatment compared with methylphenidate," said Steven Pliszka, M.D., lead investigator of the study and chief of child and adolescent psychiatry at The University of Texas Health Science Center at San Antonio. "It is important for children with ADHD to have effective treatment, because left untreated, ADHD can increase the risk of low self-esteem and social and academic failure."

Key findings of the new clinical study

In Dr. Pliszka's clinical study, 58 children diagnosed with ADHD were given Adderall, methylphenidate, or placebo for three weeks in a double-blind parallel-group design. All groups started week 1 on a once-daily dosing regimen. If the children's afternoon or evening behavior did not improve after week 1, a mid-day or 4 p.m. dose was added for week 2. Teachers rated morning and afternoon behaviors, while parents rated evening behaviors. According to teacher ratings, Adderall produced more improvements in inattentive and oppositional behaviors than methylphenidate (p less than 0.05). In addition, the psychiatrist-administered Clinical Global Impression Improvement scale, which is used to assess response to treatment, showed that more children found greater ADHD symptom relief with Adderall than with methylphenidate. In fact, 90 percent of children taking Adderall were found to be "very much improved" or "much improved" in behavior, when statistically compared with 65 percent of the methylphenidate group and 27 percent of the placebo group (p less than 0.01).

The study also showed that 70 percent of patients taking Adderall and only 15 percent of patients taking methylphenidate were still on once-daily dosing at the end of the study, based on a pre-defined dose

titration scheme. "The higher response rate for Adderall is very encouraging," Dr. Pliszka said. "Our study suggests that Adderall can be the first option for the treatment of ADHD."

In the study, both medications were well tolerated, and side effects were similar to placebo. The most common side effects associated with stimulant use are insomnia, loss of appetite, stomach pain, headache, irritability, and weight loss.

The University of Texas study was funded with a grant from Shire Richwood Inc., which manufactures Adderall.

About ADHD

ADHD affects 3 percent to 5 percent of all school-age children, and is considered the most frequently diagnosed psychiatric disorder in children and adolescents. The most common behaviors exhibited by those who have ADHD are inattention, hyperactivity, and impulsivity.

Stimulant medications -- which stimulate areas of the brain that control attention, impulses, and self-regulation of behavior -- are among the most successful treatments for people with ADHD. In fact, at least 70 percent of children with ADHD respond positively to treatment with stimulant medication.

About Adderall

Adderall is a stimulant medication for the treatment of ADHD. It has been shown to improve attention span, decrease distractibility, improve the ability to follow directions and complete tasks, and decrease impulsivity and hyperactivity.

Adderall is generally well tolerated. While adverse reactions are rare, the most frequently reported adverse reactions include anorexia, insomnia, stomach pain, headache, irritability, and weight loss. These side effects are similar to those seen with other stimulant medications used to treat ADHD. As with most stimulant medications indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exists with Adderall treatment, and, in rare cases, exacerbations of psychosis have been reported. Since all amphetamines have a high potential for abuse, Adderall should be used only as part of a comprehensive treatment program under close physician supervision.

About Shire Richwood Inc.

Shire Richwood Inc. is a subsidiary of Shire Pharmaceuticals Group plc, an emerging specialty pharmaceutical company with sales, **marketing,** and R&D operations in the U.S. and the U.K. Shire Richwood Inc. manufactures neuro-pharmaceutical products indicated for ADHD, including Adderall(R) and Dextrostat(R) (dextroamphetamine sulfate), as well as prescription products for other selected niche markets for the treatment of central nervous system disorders and metabolic bone diseases.

Please see full prescribing information on Adderall at http:/ /www.shire.com/3products/us products/adderall.html

Please see full prescribing information on Dextrostat at http:/ /www.shire.com/3 products/us products/dextrostat.html

Ritalin(R) is a registered trademark of Novartis Pharmaceuticals.

Med Ad News

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BYLINE: Humphreys, Andrew

AUTHOR-ABSTRACT:
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BODY:

With revenue approaching $ 1 billion, a broad drug delivery technology base, and a growing pharmaceutical product portfolio -- Alza is the best in the industry

Many companies would be reeling six months after a failed merger attempt, but Alza Corp. became stronger. For 1999, Alza set records in revenue, net sales, gross margins, and sales of self-marketed products. Alza launched a product that exceeded sales expectations, gained approval for three supplemental new drug applications, filed two new product applications, and entered into six technology agreements with pharmaceutical partners. And the company is well on its way to a stronger performance in 2000.

Management at Alza has set the fob lowing goals for 2000: $ 1 billion in revenue; earnings growth of at least 20%; and more than 40% growth in self-marketed products, resulting in sales of more than $ 450 million.

"We are on target to reach our year 2000 corporate objectives," says Ernest Mario, Ph.D., chairman and CEO.

With first-quarter 2000 results in, Alza reported revenue of $ 201 million, up 8%, earnings per diluted share of 30 cents, up 7.1%, and sales of company-marketed products totaling $ 80 million, up 17%.

"Our foremost strategic objective for the past six years, as longtime Alza investors well know, has been to enhance the profitability of our company through the higher margins achievable in **marketing** our own products," Dr. Mario says. "Moving aggressively into pharmaceutical sales represented a major change for Alza, making our success in this endeavor all the more exciting."

Alza's marketed product sales as a percentage of revenue has increased from 4% in 1995 to 40% in 1999. Alza officials attribute their success to their ability to shift the company's revenue stream from contract

manufacturing and royalties and fees to **marketing** their own products.

"**Marketing** our own products is a revenue stream that's within our control," says Bruce Cozadd, executive VP and chief operating officer of Alza. "We can make decisions about shifting priorities between products we market, hiring more sales representatives, striking alliances, doing more clinical trials, and starting new **marketing** campaigns. We control that revenue stream, as opposed to our contract manufacturing business and royalty business, where we are effectively reaping the rewards of decisions other companies make about their promotional efforts."

Sales of Alza-marketed products in 1999 grew 84% to $ 323.4 million, the fifth consecutive year in which sales have doubled or almost doubled. The company's top-selling product is Ditropan XL, a once-daily treatment for overactive bladder, which had 1999 sales of $ 86.9 million. The product was launched in February 1999. Ditropan XL's sales exceeded expectations by about $ 20 million, or 30% more than initially anticipated, in the face of strong competition from Pharmacia Corp.'s market-leading overactive bladder treatment Detrol.

Alza's stated strategy of concentrating on organic growth is supplemented by its ability to orchestrate profitable out licensing arrangements for its products.

In May 2000, Alza and Bayer Corp. entered into two joint-promotion accords. The terms of one pact call for Bayer to jointly promote Ditropan XL to urologists through its specialty salesforce. In addition, Alza will jointly promote Bayer's billion-dollar anti-infective drug Cipro via its specialty salesforce, primarily targeting urologists, obstetricians, and gynecologists.

According to New York-based analysts at Salomon Smith Barney, Bayer's added promotional support for Ditropan XL should spur market-share growth over time. As of April 28, Ditropan XL maintained a 23.7% share of new prescriptions compared with Detrol's 46.7% share of new prescriptions.

Detrol, a twice-daily tablet, was launched in the United States in May 1998 and generated sales of $ 328.9 million last year. According to Salomon Smith Barney analysts, the product is expected to have sales of $ 335 million in 2000, $ 360 million in 2001, and $ 390 million in 2002.

Analysts from UBS Warburg LLC in New York project that Ditropan XL will have sales of $ 150 million in 2000 and $ 200 million in 2001. Analysts did not include European sales in their estimates. Paris-based Sanofi-Synthelabo SA is expected to launch Ditropan XL in Europe this summer, where the product was filed for approval last August.

In the United States, Ditropan XL is promoted by 250 primary-care representatives and an additional 130 urology representatives. Salomon Smith Barney analysts predict that another 100 sales representatives from Bayer will be added to the promotion of the product. According to analysts, the joint promotion of Ditropan XL is a strong opportunity for Alza as the company receives additional Ditropan XL support in exchange for the cost of promoting Cipro.

The fluoroquinolone antimicrobial Cipro is indicated for treating a variety of infections, such as urinary tract infections, acute uncomplicated cystitis in females, and chronic bacterial pro statitis. Cipro generated 1999 sales of $ 1.63 billion and is expected to make $ 1.30 billion in 2000, $ 1.20 billion in 2001, and $ 1.10 billion in 2002.

The second Bayer accord calls for Alza to jointly market Bayer's Avelox in the United States to primary-care physicians. Alza will receive payment for each sales call and a percentage of sales above

specified thresholds.

Avelox was approved and launched in December 1999 as a once-daily tablet for treating acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia. The product is projected to generate sales of $ 166 million in 2000, $ 388 million in 2001, and $ 554 million in 2002.

Avelox will be promoted by Alza's 250 primary-care sales representatives who only are**marketing** Ditropan XL. Analysts rate this situation positively for Alza since the company will be reimbursed for every detail call, which is expected to be accounted for as royalties and fees. Alza's primary-care sales-force will gain an additional product to promote without associated costs.

Alza signed another agreement for one of its developed products in April with Bayer. Viadur is a once-yearly implant for the palliative treatment of advanced prostate cancer. Bayer now holds the **marketing** rights to Viadur in the United States through 2015. Alza will receive significant upfront and milestone payments, and manufacturing, patent, and trademark payments on a quarterly basis through third-quarter 2001.

Following Viadur's launch, Alza will receive royalty payments based on net sales of the product, as well as milestone payments when the drug achieves specified sales levels. Alza retains the right to buy back the U.S. commercialization rights to Viadur at the end of 2008, 2010, or 2012.

Viadur, which received U.S. **marketing** approval in March 2000, is the only product to provide continuous, 12-month testosterone suppression with a single treatment. In addition, the luteinizing hormone-releasing hormone agonist is the first approved drug to incorporate Alza's proprietary Duros implant technology.

Duros implants, one of seven Alza platform technologies (see box on page 61) are miniature titanium cylinders designed to provide continuous, osmotically driven delivery of drugs within the body for up to one year. Following implantation, the implants enable continuous, precise delivery of therapeutic compounds at rates as low as 1/100th of a drop of water daily. The cylinder protects therapeutic agents from degrading in the body and, in conjunction with Alza's proprietary formulation technology, enables a drug to remain stable for extended periods.

UBS Warburg analysts say Viadur's March approval came three months earlier than was expected. The product was filed for U.S. approval May 25, 1999. Remaining scale-up and manufacturing issues could delay the product's launch until late 2000 or early next year.

UBS Warburg analysts forecast that the once-yearly implant could generate peak sales of $ 200 million in the prostate cancer market. Viadur will compete against Lupron, an injectable product that must be administered several times a year and, therefore, has a higher cost of disease management. According to UBS Warburg, Viadur has advantages of convenience and economics, which is appealing to the heightened cost-conscious managed-care environment.

Lupron is marketed by Tap Pharmaceuticals Inc., Deerfield, Ill. The product generated 1999 sales of $ 730 million and is expected to make $ 740 million in 2000, $ 750 in 2001, and $ 760 million in 2002.

In April, Alza entered into an arrangement to jointly promote Concerta in the United States with McNeil Consumer Healthcare Co., a division of Johnson & Johnson based in Fort Washington, Pa. Concerta is an extended-release tablet indicated for the treatment of attention deficit hyperactivity disorder.

Attention deficit hyperactivity disorder is characterized by symptoms of inappropriate inattention, hyperactivity, and impulsiveness. According to the American Psychiatric Association, attention deficit hyperactivity disorder is the most common psychiatric disorder in school-age children. The condition affects 3% to 6% of school-age children and persists into adulthood for up to 60% of patients. Standard medications often require a multiple-dosing schedule throughout the day.

Alza will support once-a-day Concerta with a specialty central nervous system salesforce of 120 members who will focus on psychiatrists, neurologists, and selected pediatricians.

McNeil will deploy its pediatric and primary-care salesforces, which combined represent more than 330 sales representatives. The company already has strong established relationships in this area through promoting the over-the-counter products Children's Tylenol and Children's Motrin for pain relief. McNeil will receive payments for its sales efforts and royalties.

Concerta delivers medication with a single dose at a controlled rate of 12 hours, thereby eliminating the need for in-school or after-school dosing. Concerta combines methylphenidate -- the most commonly prescribed therapy for attention deficit hyperactivity disorder -- with a version of Alza's Oros osmotic controlled release drug delivery technology.

In May, Alza and Crescendo Pharmaceuticals Corp. received an approvable letter from the Food and Drug Administration for Concerta. The product's new drug application was submitted July 21, 1999. Concerta is being developed by Alza on behalf of Crescendo. Crescendo was formed by Alza for the purpose of selecting and developing human pharmaceutical products for commercialization, most likely through in-licensing to Alza.

Analysts at Salomon Smith Barney believe that J&J is an excellent partner for Concerta's launch, which is anticipated this fall. Analysts say this structure is advantageous for Alza, because it allows the company to focus on a smaller physician group, thereby creating significant attention.

UBS Warburg analysts project that Concerta should be launched this August. The New York based analysts believe that Concerta has sales potential of $ 200 million to $ 300 million within five years of launch.

Analysts say there will be two competitors for Concerta that could reach the market as early as 2001: **Ritalin** QD and Attenade. Novartis Pharmaceuticals Corp., East Hanover, N.J., is developing **Ritalin** QD, which is in Phase III clinical trials. Attenade is in Phase I/II clinical trials by Celgene Corp., Warren, N.J.

Alza operates two business units: Alza Technologies and Alza Pharmaceuticals. Alza Technologies encompasses research and product development for third party clients and Alza Pharmaceuticals, and regulatory activities for products incorporating the company's proprietary drug delivery technologies and/or technologies licensed from third parties. The business unit manufactures products incorporating Alza's drug delivery technologies for third-party clients and for Alza. Alza Pharmaceuticals commercializes products developed by Alza Technologies and products acquired from third parties.

Alza Pharmaceuticals has three business units: an oncology business unit with a specialty U.S. salesforce, a urology business unit, and a central nervous system unit, which is being assembled in anticipation of Concerta's launch.

Because Alza Technologies can create more products than Alza Pharmaceuticals can successfully bring to

market, license arrangements with strong partners are necessary. Alza's recent strategy of out-licensing products from its pipeline complements its initiatives of acquiring products to fill gaps in its portfolio. In 1997 and 1998, Alza acquired the U.S. **marketing** rights to: Mycelex Troche, an antifungal agent from Bayer; Elmiron for bladder pain relief and three other urology products from Baker Norton Pharmaceuticals Inc., Miami; and Urispas for incontinence from SmithKline Beecham, Philadelphia.

For 1999, Alza's total revenue increased 23% to $ 795.9 million compared with 1998. Net income decreased 16% to $ 91 million, with earnings per diluted share down 17.8% to 88 cents. The decrease in income and earnings per share are attributed to one-time costs associated with the defunct merger with Abbott and other one-time charges.

In January 2000, officials from Alza and Abbott Laboratories, Abbott Park, III., formally terminated their merger arrangement. The companies additionally agreed to cease Abbott's joint promotion of Ditropan XL and Abbott's right of first negotiation to jointly market Concerta.

The two companies announced their intention to merge June 21, 1999. Despite considerable efforts, Alza and Abbott were unable to reach an agreement with the Federal Trade Commission that would satisfy the commission's antitrust concerns relating to the merger and particularly for Viadur.

Dr. Mario does not foresee another merger opportunity soon. "Our share price is going up, which is enhancing our value, which may present for us the opportunity to be the acquirer, opposed to the acquiree," he says.

Salomon Smith Barney analysts predict that during the next two years, Alza's revenue and earnings growth will be more than 25% per year. For 2000, analysts project revenue of $ 961 million with the company's market capitalization at $ 4.81 billion.

Established in 1968, the Mountain View, Calif.-based company's revenue has grown from $ 162.3 million in 1991 to about $ 800 million last year.

With seven technology platforms, Alza's drug delivery expertise is one of the broadest in the industry. Alza spent $ 183.6 million on research and development in 1999. The company's pipeline includes seven line-extension projects, three new products in development, and nine early-stage drugs. Alza executives are concentrating on developing line extensions for marketed products.

"Like other pharmaceutical companies, we realize that one of the ways we could substantially expand our revenue base going forward is by taking some of the products we already have on the market or in late-stage development and creating new indications for those products," Mr. Cozadd says. "That doesn't mean we're not working on new things, too, but we don't want to overlook the potential to dramatically expand sales of key brands we already have."

During 2000, the company plans to initiate a Phase III clinical program to evaluate the potential of Doxil in treating multiple myeloma. Doxil additionally is in development for the treatment of breast cancer, a new indication that could generate $ 80 million in peak sales.

Doxil was acquired through the March 1999 purchase of Sequus Pharmaceuticals Inc. Alza additionally gained Sequus' Stealth advanced liposomal technology.

A clinical program is planned for Concerta in managing cancer-related fatigue. In the urology setting, Alza is exploring studies of Elmiron in treating chronic pelvic pain syndrome, a condition that affects between 6

million and 12 million American men. UBS Warburg analysts say the market potential for this indication is more than $ 500 million.

Alza Technologies has produced more than 25 drug delivery-based commercial products. According to Alza management, Phase III clinical trials are to be initiated in midyear for E-Trans fentanyl, for acute pain management. E-trans fentanyl previously was under development by Janssen Pharmaceutica Inc., Titusville, N.J., and would be the first commercial product based on Alza's proprietary E-trans electrotransport technology to reach the market.

Alza has several technology-based deals in the works with other pharmaceutical companies. One accord is with Pfizer Inc., New York, for an Oros version of an undisclosed Pfizer product. Alza has inked its first pact with a major pharmaceutical company for a product using the liquid Oros system.

There is a continuing development program with Pharmacia for a Depot formulation of an undisclosed product. Alza's proprietary bioerodible polymer Depot injection technology is designed for the sustained delivery of biologically active agents for one week to one month. UBS Warburg analysts have speculated that the Pharmacia product is a woman's health product with multihundred-million dollar sales potential.

In February, Alza officials discussed their plans to enhance the company's product development pipeline by adding new early-stage projects in the urology,

oncology, central nervous system, and pediatric areas as well as other areas where they believe that their technology has the potential to improve current standards of care.

Alza's osmotic and D-Trans drug delivery systems have been incorporated into more than two dozen products that are marketed worldwide, including the antihypertensive agent Procardia XL and the diabetes drug Glucotrol XL for Pfizer, the smoking-cessation patch NicoDerm CQ for Pittsburgh-based SmithKline Beecham Consumer Healthcare, and the pain-reliever Duragesic for J&J.

Royalties, fees, and other revenue for 1999 were $ 227 million, slightly lower than in 1998. Royalties from Duragesic, NicoDerm CQ, and Glucotrol XL increased, and royalties on Procardia XL continued to decline.

For the first three months of 2000, the 17% sales growth of Alza-marketed products reflected a 49% growth in Ditropan XL sales and a 60% growth in Ethyol sales compared with first-quarter 1999. Ditropan XL's first-quarter sales came in at $ 32.8 million, $ 3 million more than predicted. Analysts forecast continued growth for Ditropan XL; the product is expected to reach $ 155 million in 2000. The product is projected to be launched later this summer in the United Kingdom.

What makes Alza special

* Seven commercialized drug delivery technology platforms; largest array of drug delivery platform technologies in the industry

* Established pharmaceutical technology development infrastructure

* More than 25 drug delivery-based commercialized products

* Steady income streams from well established products: Doxil, Elmiron, Mycelex Troche, Testoderm TTS, and Ethyol

* Revenue from new product launches: Ditropan XL generated more than $ 85 million in sales, 30% more than anticipated

* Solid pipeline: Seven line-extension projects, three new products in development, and nine early-stage drugs

* Strong partnerships with big pharma: six new development deals signed in 1999, including pacts with Pfizer Inc. and Pharmacia Corp., as well as **marketing** arrangements with Bayer Corp. and McNeil Consumer Healthcare Co.

* Stated target of 20% earnings-pershare growth

* Stated target of $ 1 billion in revenue in 2000

* Total salesforce of 1,500, including representatives from joint-promotion partners

Alza's drug delivery technologies

Alza was the pioneer and a recognized leader in the development of innovative drug delivery technologies. Alza's therapeutic systems are designed to provide controlled, predetermined rates of drug administration. By administering drugs in preset patterns and by alternative routes, the company's advanced dosage forms, called therapeutic systems, can add to the medical and economic value of drug therapies. Alza's drug delivery technologies minimize a drug's unpleasant or harmful side effects, optimize its beneficial actions, simplify drug therapy, increase patient compliance, and in some cases improve a patient's quality of life.

* Depot injection -- a bioerodible polymer injection technology that is in preclinical development, designed as a platform to deliver therapeutic agents over a period of up to one month. The bioerodible Depot gel has been demonstrated, when injected into the subcutaneous tissue of animals, to deliver therapeutic agents with little or no drug burst upon injection.

* D-Trans -- a passive transdermal therapeutic system that provides controlled delivery of drugs directly into the bloodstream through intact skin. D-Trans products are thin, multilayer systems in the form of small adhesive patches that combine a drug reservoir with a polymer membrane to control drug release to the surface of intact skin, and then through the skin into the bloodstream.

* Duros -- an implant technology designed to enable the delivery of therapeutic agents, including potent small molecules, peptides, proteins, DNA, and other bioactive macromolecules for periods of one month to one year. Duros systems use an osmotic engine approach similar to that used in Oros systems. Products incorporating Duros have the potential to deliver drugs to subcutaneous sites for systemic therapy or to specific tissues.

* E-Trans -- an electrotransport system that is designed to deliver drugs across intact skin through the use of an electrical potential gradient. E-Trans systems are small, easy-to-apply delivery systems consisting of an adhesive, a drug reservoir, electrodes, and a power source/controller. The systems are designed to deliver potent therapeutic agents through the skin, and can be designed for patterned or on demand delivery.

* Macroflux -- a skin interface technology that is designed to increase drug transport across the skin and enable delivery of larger molecular weight compounds, including proteins, peptides, and vaccines. This

new technology, which uses an array of microprojections to painlessly open channels for drug transport in the outermost layer of the skin, may be used alone or may be used to enhance Aiza's D-Trans and E-Trans technologies.

* Oros -- therapeutic systems that are designed for oral administration, including the push-pull, push-stick, and elementary osmotic pump systems. Oros products resemble conventional tablets or capsules, but use an osmotic mechanism to provide preprogrammed, controlled drug delivery to the gastrointestinal tract. Oros products comprise a polymer membrane with one or more laser-drilled holes surrounding a core containing the drug, with or without osmotic agents. Water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the drug core, causing the drug to be released in solution or suspension at a controlled rate out of the laser-drilled hole. Alza is developing a liquid Oros system designed for the delivery of emulsions or microparticulate suspensions of highly insoluble drugs or polypeptides.

* Stealth liposomes -- incorporate microscopic lipid spheres used to encapsulate and deliver medications to areas of disease in the body. Stealth liposomes are designed to stay in the blood circulation for extended periods after intravenous administration. The. prolonged circulation time enables the liposomes and their pharmaceutical contents, such as small molecules, proteins, peptides, oligonucleotides, and genetherapy vectors, to concentrate in diseased tissues. This site-specific delivery may result in increased efficacy and reduced toxicity for many potent medications.

An Alza exclusive

Ernest Mario, M.D., chairman and CEO, and Bruce Cozadd, executive VP and chief operating officer, discuss their strategy for the future of Alza in an exclusive interview with Med Ad News.

Med Ad News: Alza has stated a goal of generating $ 1 billion in revenue in 2000; how does the company intend to reach this milestone?

Mr. Cozadd: We expect our reported revenue for 2000 to be between $ 900 million and a $ 1 billion. We're experiencing growth in all major parts of our business right now. For the Alza Technologies business, we had about $ 370 million in total revenue last year. We're experiencing growth from royalties, driven by Duragesic, Nicoderm CQ, and Glucotrol XL. We're generating an increase in contract manufacturing revenue. We are continuing to sign deals, which bring in research and development revenue; so that portion of our business also is growing.

The Alza Pharmaceuticals side of our business, which had revenue of about $ 430 million last year, is experiencing a dramatic increase. Sales from our self-marketed products -- Ditropan XL, Elmiron, Doxil, and Ethyol -- are growing. The launch of Concerta this year will add new sales. Both parts of our business, including Alza Technologies, are growing at a rapid pace, and coming off $ 800 million in 1999 in total revenue, should put us in the $ 1 billion range.

Med Ad News: How large of a sales-force can Alza manage as an independent entity?

Dr. Mario: I don't think there's necessarily a limit, depending on the category and the target audience. In the urology area, 150 or so would be sufficient. Our own salesforce, which is about 700, and the 800 sales representatives from our joint-promotion arrangements, give us 1,500 people who are selling Alza marketed products.

Mr. Cozadd: In early 1999, we made the decision that we couldn't manage a growing unified salesforce.

We decided to break up the salesforce into specialized salesforces. This year, we took an additional step, not only of having specialized sales groups, but breaking the sales and **marketing** organization into business units. For example, the urology business unit will make decisions across sales and **marketing** for their product portfolio. In the past, all **marketing** functions reported through one person and all sales functions reported through one person.

Med Ad News: What is Alza's strategy for product acquisitions and license arrangements?

Mr. Cozadd: We will make the decision as to which products to keep and which ones to license out based on whether or not we have the ability to sell in that therapeutic category. We will base our assessment on the relative economic advantage to the company of launching a product ourselves, or taking the best available deal from outside. In the case of Viadur, an argument can be made that we had the capability to take the product to market, given our urology specialty salesforce, but the deal with Bayer was there and it gave us a better economic return on the product while allowing us to continue focusing on Ditropan XL, which is still obviously at the infancy of its product life cycle. The message out of Alza Technologies is that we can create more products than we can commercialize ourselves, so we will continue to do some out-licensing.

On the Alza Pharmaceuticals side, where we're focused on sales and**marketing,** we'll take what we can from Alza Technologies and we'll supplement, as all pharmaceutical companies do through in-licensing, where we have holes in our portfolio. The fact that we out-license and in-license has to do with the two different business units, and the decisions we make are very much based on product by product.

Med Ad News: Why did you select McNeil Consumer Healthcare as a **marketing** partner for the attention deficit disorder drug Concerta?

Dr. Mario: This is a new therapeutic category for us. When we looked at the set of doctors we would have to educate about our new product for attention deficit disorder, we realized that we needed to get to pediatricians, but we also needed to play in the central nervous system field with psychologists and neurologists. The idea was to simultaneously build a pediatric salesforce and a central nervous system salesforce, which was something that we planned on, and something that we knew we could accomplish, but we realized that with only one product in that basket, the ideal configuration would be to take a partner to address one of those markets and leave us to address the other one.

In the case with McNeil Consumer Healthcare, the combination of their willingness to put a large pediatric salesforce on our product, their sterling reputation with pediatricians, which we think is important in this category, and the financial terms we were able to put in place, we've got a fantastic combination. They'll focus on pediatricians. We'll be able to create a more focused and somewhat smaller central nervous system group that can sell Concerta, but also will be available for other products, either through in-licensing or coming out of our own pipeline.

Med Ad News: After Concerta, what does Alza's near-term pipeline hold? Mr. Cozadd: Our late-stage development pipeline right now has E-Trans fentanyl, which we had been developing for a number of years with Janssen. E-Trans fentanyl is now back in Alza's hands. We are taking that product into Phase III trials for the treatment of postoperative pain. We know that's a very large market, but we think we can get to market relatively quickly with a highly differentiated product.

Med Ad News: Where will Alza be in five years?

Dr. Mario: We have been able to effect a transition from a client laboratory, technology-driven business

where we created a product for other people, to a portfolio company with a very strong technology base. Next is an expansion into additional therapeutic categories.

We'll be dealing with bigger molecules for delivery. I envision us moving into the rest of the world -- markets where we aren't now. We have a very small operation in Canada, we have nothing going on directly in Europe or in the Far East. The United States is about 30% to 35% and the rest of the world is 65% or 70%, so there's plenty of room for us take our products into these other markets, either directly or through partnership. We're very optimistic about the future of this company.

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HEADLINE: PSYCHOTROPICS AND KIDS : Use of drugs in treating ADHD sets off new debate about finding the right therapy for children; attention deficit/ hyperactivity disorder; Statistical Data Included; Illustration

BYLINE: Magill-Lewis, Jillene

BODY:

Unless you were hiding under a rock for the past few months, you could not have missed all the publicity that attention deficit/ hyperactivity disorder (ADHD) and its associated treatments--most notably methylphenidate (**Ritalin,** Novartis)--have been getting.

There have been a few reports of severe side effects and deaths associated with methylphenidate. Most of the recent media reports were sparked by an article in the February issue of the Journal of the American Medical Association (JAMA), highlighting huge increases in psychotropic prescriptions dispensed for preschoolers.

This issue can be a bit confusing, and these news stories may have prompted concern and questions from your patients.

The drugs in question

The National Institutes of Health noted in a recent consensus statement entitled Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder that methylphenidate (MPH) is the most commonly prescribed and the most studied ADHD medication. It has been shown to be both safe and effective, at least in short-term use (less than one year).

MPH has been extensively studied in children, and it is indicated for treatment of ADHD. The product labeling further stipulates that therapy with MPH be part of a complete treatment program that involves psychological, social, and educational therapies. This drug has been used to treat ADHD for decades.

That said, it is still unclear exactly how MPH works. It has been presumed that MPH stimulates the brain stem and the cortex, although this has yet to be proven. However, a newly published study does support this theory. In the study, motor cortex activity was measured in both ADHD-diagnosed and ADHD-free children. The ADHD group demonstrated less intracortical inhibition than the control group, and researchers surmised this may be the cause of hyperactivity observed in the ADHD group. Additionally, brain scans of the ADHD group after administration of MPH resulted in a correction of the intracortical

inhibition, indicating the mechanism of action for MPH's calming effects.

One of the main drawbacks to MPH is its short half-life, often necessitating two to three doses per day. Since most children taking MPH are in school, a large percentage of them will need to take a dose during school hours. This creates a potential diversion problem, and it may lead to a feeling of stigma for the kids. Trying to circumvent this, Novartis developed **Ritalin** SR, a sustained-release tablet that lasts approximately eight hours. The manufacturer is also working on a once-daily MPH tablet, **Ritalin** QD, which is now in phase III trials. The company hopes to have the product on the market in 2001.

A partnership between Novartis and Noven Pharmaceuticals Inc., a manufacturer that specializes in transdermal drug products, has produced a 24-hour MPH patch (MethyPatch). The patch is designed to bypass some of the problems associated with oral formulations of MPH. The once-daily dosing eliminates the need to take medications during school, and the transdermal form may deter abuse. Also, the drug may be easily discontinued by removing the patch. Noven announced in March that the patch had completed phase II clinical studies and would enter phase III trials later this year. A New Drug Application is anticipated for 2001.

Another company taking its share of the ADHD market is Mallinckrodt Inc. The firm has been a major source of methylphenidate. Mallinckrodt has taken things a step further by introducing its own drug products, including Methylin (methylphenidate). By so doing, the firm has essentially cut out the middleman and can offer a brand name with a generic price as an alternative for **Ritalin.**

Mallinckrodt has expanded into the ADHD market even more by establishing a partnership with SmithKline Beecham to comarket dextroamphetamine (Dexedrine Spansules and tablets). And now, the company has received Food & Drug Administration approval for an extended-release methylphenidate, Methylin ER.

Another extended-release formulation of MPH is Concerta, to be comarketed by ALZA and McNeil. The tablets use osmotic controlled-release technology (OROS), designed by ALZA, to release the drug in three phases over 12 hours. The idea is to provide an initial dose of MPH in the morning, followed by a continual dose throughout the day, and ending with a tapered effect after school. Results of the most recent Concerta study indicate it is at least as effective as immediate-release MPH taken three times daily. Side effects reported were consistent with those normally experienced with MPH treatment.

Shire Pharmaceuticals now has about 30% of the ADHD market, according to Stefan Antonssen, v.p. of **marketing.** Adderall, a combination of dextroamphetamine sulfate and saccharate with amphetamine sulfate and aspartate, is its current product for ADHD. Sales of Adderall have climbed steadily as research and experience with the drug continue to prove its safety and efficacy.

Antonssen acknowledged the quandary some parents are in where drugs for ADHD are concerned. Proving Adderall's safety has been a primary goal for Shire. "Five published, clinical studies in peer-reviewed journals have established the safety and efficacy of Adderall," he said. Referring to the most recent study, he added, "And now there is evidence of increased efficacy of Adderall over methylphenidate."

This latest study compared a morning dose of Adderall with a morning dose of immediate-release MPH. More doses of either drug were added if needed to control ADHD symptoms, or reduced in the event of adverse effects. Results indicated Adderall may be more effective than MPH, even if MPH is given two or three times daily.

Adderall has a similar side effect profile to MPH and a longer duration of action. Antonssen believes

Adderall is now clearly a first-line agent for ADHD. Pliszka, lead investigator for the study, agreed: "Our study suggests that Adderall can be the first option for the treatment of ADHD."

New developments

Shire is working on a couple of other products for ADHD. One of them is SPD 420, a compound created by Cortex Pharmaceuticals Inc. Formerly named AMPAKINE CX516, this is one of a new class of drugs called AMPAKINEs. These increase the efficiency of glutamate binding to the AMPA glutamate receptors, promoting greater current flow. Among other things, this seems to result in improved memory function and attention. SPD 420 will be evaluated in ADHD patients in an upcoming phase II study.

Tomoxetine (Eli Lilly & Co.) is a new pharmaceutical designed specifically for ADHD. A noradrenergic reuptake inhibitor, tomoxetine attacks the problem from a different route. Study results suggest it alleviates ADHD symptoms by increasing norepinephrine levels. The compound is in phase III trials.

Fletcher Taylor, M.D., a psychiatrist with a private practice in Tacoma, Wash., studied modafinil (Provigil, Cephalon) in adult ADHD patients. The results of his study were presented at an American Psychiatric Association (APA) meeting in May. When compared with dextroamphetamine, modafinil was equally as effective, he reported. Originally approved for narcolepsy, modafinil has a low addiction potential. Because of this, Taylor hopes the drug will be a valuable treatment option for ADHD, and possibly a first-line agent. Cephalon is preparing to conduct phase III studies of modafinil in children with ADHD.

With the market for ADHD products estimated at $ 670 million annually (see Figure 1), it's easy to see why drugmakers are jockeying for first position in the ADHD race. In fact, Alza plans to introduce Concerta just before the start of the school year, so it will be available during the "peak season" for methylphenidate. Over 200 reps will be targeting pediatricians, psychiatrists, neurologists, and family practice physicians to get the word out.

Apparently the first parent-teacher conferences provoke a slew of new prescriptions for the drug. Caron Mosey, a second-grade teacher in Michigan, explained, "Generally, teachers do stimulate the process. They spend lots of time with children in a different setting [than parents]. School requires lots of sitting and focusing on tasks." Because of this, teachers often see the symptoms of ADHD before parents do.

So what exactly is ADHD?

According to the National Institute of Mental Health (NIMH), ADHD is actually a group of neurobiological disorders. These disorders are characterized by hyperactivity, impulsivity, and inattention. However, not all patients exhibit all three symptoms. For example, one type of ADHD, termed "predominantly inattentive type," is distinguished by a lack of hyperactivity. This disorder may also be referred to as "attention deficit without hyperactivity" or "ADD," although ADD is also used interchangeably with ADHD, especially in the lay media.

The incidence of ADHD varies according to source. The National Attention Deficit Disorder Association (ADDA) estimates that between 4% and 6% of Americans are affected; NIH believes 3% to 5% of kids have ADHD; and Children and Adults with Attention Deficit/ Hyperactivity Disorder (CHADD) weighs in with 1% to 20% of school-age children having ADHD to some extent. So why the disparity?

Steven Pliszka, M.D., chief of child and adolescent psychiatry at the University of Texas Health Science Center at San Antonio, explained that ADHD cases range from the very mild to the very severe. The incidence rate hinges on the diagnosis, and different investigators will come up with different numbers,

depending on how they define ADHD. Very severe cases of ADHD occur in about 2% of the population. And the rest? "Five percent to 8% is probably the best estimate," he said.

The cause of ADHD is unknown. NIH has gathered evidence that there may be genetic or environmental risk factors for developing ADHD. Studies to determine its etiology have found a correlation between certain neurotransmitters and the disorder, but the exact mechanism remains elusive. Recently, researchers have linked a streptococcal infection with ADHD.

Media overkill?

"Media people have no concept of how serious [ADHD] is," said Ellen Kingsley. An Emmy Award-winning journalist herself, Kingsley retired when her son was diagnosed with ADHD eight years ago. She explained that it is in the best interests of the television networks to create a controversy even if there isn't one, including "this whole issue of drugs versus no drugs [in ADHD]."

However, any investigation into ADHD will reveal that it is a very polarized issue, with few folks riding the fence. On the one side are a few outspoken psychiatrists, parents, and other professionals, including optometrists, who believe ADHD is overdiagnosed and psychotropics are overprescribed. On the other side are the majority of psychologists and psychiatrists, parents, teachers, and (of course) drugmakers who believe ADHD is a legitimate condition that responds well to drug therapy.

Those opposed...

Understandably, many parents are reluctant to have their kids taking stimulants, antidepressants, and the like. Worries about side effects and abuse top the list of concerns, according to ADDA. News reports have focused on parents who share these worries, highlighting their search for such nonpharmacological therapies as neurofeedback and newfangled diets.

According to Brad Habermehl, O.D., an optometrist with the Vision Therapy Group in Flint, Mich., about 30% of all children have a binocular vision problem that prevents them from focusing, resulting in double vision, blurred vision, and eye strain. This inability to focus causes ADHD-like symptoms in this population, and, Habermehl believes, leads to a misdiagnosis of ADHD. "Nine out of 10 have been diagnosed with ADD or ADHD," he said. He treats the condition by training the eyes to focus normally through visual exercises.

Peter R. Breggin, M.D., a psychiatrist and founder of the International Center for the Study of Psychiatry and Psychology (ICSPP), said, "ADHD is a diagnosis that's false." It is his opinion that the symptoms of ADHD are really signs of another problem that should be pinpointed and treated. For example, if a child is having difficulties in school, the solution may be as simple as finding a different teacher who can interest and engage the child.

Breggin is completely opposed to treating ADHD with medications. Referring to methylphenidate, he said, "It crushes spontaneity, curiosity, and play." He believes a conspiracy of sorts exists between drug manufacturers and APA, which results in millions of children being put on drugs and multimillions in profits for the drug companies. In fact, Breggin is a primary consultant in a class action lawsuit against Novartis Pharmaceuticals, APA, and CHADD.

Those in favor...

Kingsley emphatically disagrees with Breggin. "We're where depression was 10 years ago. We know now

it's a neurobiological disorder that is correctable, not curable." Kingsley, who created Additude Magazine with the goal of destigmatizing and detrivializing ADHD, said the problem is not just that kids with this disorder have trouble paying attention in class. "Their thinking isn't organized, working memory is affected."

Nor is the problem a parenting issue. "Bad parenting doesn't cause ADD, and good parenting doesn't cur it," said Kingsley. Initially, she resisted medicating her son, even with the backing of her husband, a psychiatrist. Now, however, she believes medication saved her son's life. "Without it, I don't know what would have happened to him."

The vast majority of experts do believe ADHD is a valid disorder that is most effectively treated with medications and therapy, as evidenced by NIH's consensus statement. The statement is a product of an NIH conference on ADHD held in 1998 and attended by over 1,000 experts in pediatrics, psychology, education, epidemiology, neurology, and psychiatry.

This spring, Hillary Rodham Clinton announced a plan to address psychotropic use in kids. Working with the FDA, NIMH, and the Department of Education, the First Lady intends to create educational materials, clarify the pediatric labeling of psychotropics, and research the effects of these drugs in young children. Also in the works is a National Conference on Treatment of Children with Behavioral and Mental Conditions, scheduled for this fall.

The American Academy of Family Physicians and the American Academy of Pediatrics have joined forces to establish and disseminate new guidelines for the pediatric diagnosis of ADHD.

Two Senators, Christopher Dodd (D, Conn.) and Mike DeWine (R, Ohio), have been pushing for increased pediatric research by targeting both the FDA and NIH. These same senators are responsible for a rule allowing extra patent protection for drug manufacturers that conduct pediatric research. Manufacturers that do such research may obtain six months' extension of exclusivity.

The FDA has asked several drug companies to do pediatric testing of certain psychotropic drugs. As of May 2000, the agency had issued several written requests for pediatric research on "neuropharmacological drug products." Manufacturers are not required to do the studies, but the market exclusivity is an incentive to do so.

'Vitamin R'

According to the NIH consensus statement, examination of available research did not reveal a conclusive propensity for drug abuse in ADHD children treated with stimulants. Studies on the subject came to varying conclusions. However, untreated ADHD does lead to drug abuse in older children.

Illicit use of stimulants is what concerns the Drug Enforcement Administration. The DEA lists methylphenidate as a drug of concern, and amphetamines have long been an abuse problem. Methylphenidate abuse has been on the rise, particularly among teenagers, according to the DEA. The drug has been used by this group for weight loss, as an aid to studying, and as a euphoric. Sometimes referred to as "vitamin R," methylphenidate is often crushed and then inhaled intranasally. However, the most worrisome problem is the practice of injecting the dissolved tablets intravenously, which can lead to serious lung and eye damage.

The DEA has received increased reports of thefts of methylphenidate recently. Thefts from schools now contribute substantially to the illicit supply of this drug. This is of special interest to the DEA because

schools are not regulated with regard to controlled substances. Terrance Woodworth, deputy director of the DEA Office of Diversion Control, testified at a House subcommittee hearing in May. He summarized the diversion problems of methylphenidate, focusing on the increased availability and vulnerability of supplies of the drug in schools. Proper storage and handling of controlled medications need to be addressed, he said.

The U.S. Pharmacopeia decided at its April 2000 meeting to help create guidelines for proper management of medications by schools. Strategies for storage, administration, and disposal of students' medications are among those to be developed. The American Pharmaceutical Association also addressed this issue as a New Business Proposal during its house of delegates meeting this past March. The proposal urges pharmacists to get involved in creating these guidelines.

Advice from the experts

Whether ADHD is simply a blanket diagnosis for many other problems, a scam to fatten the pockets of pharmaceutical companies and professional organizations, or a true neurobiological disorder, the end result is that millions of kids are being treated with psychotropic medications. The bottom line is, Are these drugs harming or helping kids? As pharmacists, what can you do to help manage their drug therapy and help prevent adverse effects?

Pharmacists at Bridgeport Pharmacy in Lakewood, Wash., work with the pediatric group in their building to evaluate the need for drug treatment of ADHD. The pharmacy compounds methylphenidate or Adderall into capsule form and creates a duplicate placebo prescription. Only the pharmacy knows which capsules contain the drug. In addition, the patients' parents are given a monitoring sheet to track the effects of the treatment. Jerry Berndt, R.Ph., v.p. and manager of the pharmacy, said this double-blind, placebo-controlled test "alleviates all these unnecessary prescriptions for **Ritalin** and Dexedrine. The doctors are prescribing for the kid, not the parent or the teacher."

Roselle Sanderson, the technician at Bridgeport Pharmacy, has been compounding these test capsules for several years. When asked about the results, she replied, "Probably 85% respond to medication."

Steve Clement, R.Ph., of Copper Bend Pharmacy in Belleville, Ill., plans to initiate a similar program in his pharmacy. Clement already is part of a team effort to treat ADHD, and he works with local physicians to coordinate pharmaceutical care for these patients. He spends five to 15 minutes counseling new patients on their ADHD medication. "Educate before you medicate--that's very, very important." He focuses on side effects, proper storage, and dosing.

Clement also discusses the abuse potential of the stimulants, particularly when the prescriptions must be taken to school. He recommends parents count all controlled medications and store them where they won't easily be pilfered. He does his part by monitoring refills closely.

Patient assessments are an important part of Clement's ADHD program. He often does follow-up calls with new patients. He checks to see whether the medications are working by asking questions about specific behaviors. "There should be almost immediate improvement," he said. In addition, most patients take a break from medication during the summer to allow for reevaluation and for growth spurts.

When asked if he felt stimulants were overprescribed, Clement responded that it was difficult to tell. His pharmacy fills three to five new Rxs per week for pediatric psychotropics, with a peak at the beginning of the school year. The vast majority of prescriptions are for methylphenidate. "I feel sometimes parents insist on meds, but the pediatricians that deal with [ADHD] a lot adhere to [diagnostic] criteria." He added that

his ADHD patients are school-age kids, not preschoolers.

John Markowitz, Pharm.D., BCPP, and C. Lindsay DeVane, Pharm.D., BCPP, have coauthored The **Ritalin** Handbook. (For information on the book, call 1-800-253-9104.) A resource for patients, the book contains a wealth of information that is not limited to methylphenidate. "It incorporates a lot of information that many pharmacists and some doctors may not know," added Markowitz. An example of this is the result of recent research, done by Markowitz and DeVane, that discovered a new metabolite of alcohol and methylphenidate: ethylphenidate. The compound appears in small amounts when the substances are consumed together. Its significance is not yet known.

Counseling is best

Markowitz agreed with Clement that counseling is probably the best way for pharmacists to help their ADHD patients. In addition, he noted that some R.Ph.s are skeptical about the validity of ADHD and may be reluctant to fill stimulant Rxs. He suggested pharmacists learn more about the disorder and warned that more and more adults will be diagnosed with ADHD in the future. "If you're worried about abuse," he said, "look at the frequency of prescriptions and other characteristics. Frequently, if someone is abusing one drug, he or she is abusing something else."

Maria Llana Posey, M.A., Pharm.D., BCPP, is a psychotherapist and clinical pharmacist at Scott & White Memorial Hospital in Temple, Texas, department of psychiatry, division of child and adolescent mental health. She echoed Markowitz's concern over labeling patients as abusers. "Some pharmacies are not interested in carrying Dexedrine because of the concern of abuse. I understand this, but all stimulants can be misused, so really there is no reason to pick one to be more concerned about."

Posey is more concerned with dosing stimulants properly. "Some M.D.s will write b.i.d. or t.i.d. on the prescription," she said. This worries her because it can be very confusing. "Usually, b.i.d. means morning and bedtime, but for a stimulant it likely means morning and lunchtime. For stimulants, t.i.d. most likely means morning, lunch, and after school."

Posey recommended clarifying the directions with the patients' physicians. "I have had a few folks give the child a bedtime dose and then complain that the child is not sleeping. Some children, however, do take a bedtime dose--I know it sounds odd, but it is really helpful for them." As for growth suppression with stimulant use, she said this side effect has not yet been proven. Although it has been common to give kids a drug holiday during the summer, "Many children are taking medication seven days a week throughout the year."

Posey's other concern was that some pharmacists who think a dose of a medication may be too high should discuss this with the physician, not the patients. "Sometimes, the dose does get up there and we use higher than expected doses, but checking it out is a great idea."

Peter Jensen, M.D., director for the Center for the Advancement of Children's Mental Health, had this advice for pharmacists confronted with a psychotropic prescription for young children: "Be sure they've had an expert evaluation."

Jensen identified psychiatrists and neurologists as practitioners qualified to make this sort of evaluation, and he added, "If you find you're filling lots of prescriptions for psychotropics and nothing else, advise parents to consult with an expert."

Jillene Magill-Lewis, R.Ph. the author is a medical writer based in Tacoma, Wash.

PR Newswire

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HEADLINE: Celgene Announces End of FTC Waiting Period; d-Methylphenidate License Agreement with Novartis Now Effective;
Milestone Triggers $10 Million Payment to Celgene

DATELINE: WARREN, N.J., June 12

BODY:

Celgene Corporation (Nasdaq: CELG) announced today that its exclusive worldwide (except Canada) license agreement with Novartis Pharma AG for the development and **marketing** of d-methylphenidate, its chirally pure version of **Ritalin**(R), has become effective with the expiration of the 30-day waiting period required under the Hart-Scott-Rodino (HSR) Pre-Merger Notification Act on June 10, 2000.

"With the HSR waiting period behind us, we will quickly establish the joint Novartis-Celgene development committee that will oversee the further development and commercialization of this compound. This milestone triggers a $10 million payment under the agreement. Our next major objective is to submit our New Drug Application (NDA) in the third quarter of this year," said Sol Barer, Ph.D., President and Chief Operating Officer of Celgene.

Under the terms of the agreement, Celgene granted its intellectual property rights to the chirally pure version of **Ritalin** and to a long acting formulation of **Ritalin.** This formulation will eliminate the mid-day dose, which has been identified by physicians, parents and school staff as a significant unmet medical and market need.

Under the license agreement, Novartis is to fund all remaining development required for the regulatory approval process and to cover expenses associated with the commercialization of the product. A joint development committee will direct the commercialization and regulatory strategies regarding the new drug including the continuation of **marketing** trials to amplify its safety and efficacy profile. As previously announced, Celgene will receive substantial milestone payments upon submission and approval of the d-methylphenidate products as well as royalties on all formulations of the **Ritalin** product line.

Celgene Corporation, headquartered in Warren, New Jersey, is an independent biopharmaceutical company engaged in the discovery, development and commercialization of small molecule drugs for cancer and immunological diseases. Please feel free to visit the Company's website at http://www.celgene.com .

This release contains certain forward-looking statements which involve known and unknown risks, delays, uncertainties and other factors not under the Company's control which may cause actual results, performance or achievements of the Company to be materially different from the results, performance or other expectations implied by these forward-looking statements. These factors include results of current or pending research and development activities, actions by the FDA and other regulatory authorities, and those factors detailed in the Company's filings with the Securities and Exchange Commission such as 10K, 10Q and 8K reports.

TheStreet.com

June 6, 2000 Tuesday

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HEADLINE: Attention Class, Alza Has Just the Medicine for You

BYLINE: By Dane Hamilton, Staff Reporter

DATELINE: June 6, 2000 1:02 PM ET

BODY:

Alza (AZA:NYSE) has a message for your kids: Just say yes.

The upstart drugmaker, which took a big chunk out of the incontinence-drug market developed by Pharmacia (PHA:NYSE), is now targeting another potentially lucrative niche: treating childhood hyperactivity. And analysts are expecting another success.

Alza turned a corner last month, when it won preliminary Food and Drug Administration approval to sell Concerta, a timed-release version of a generic standby for treating hyperactivity in children and adolescents. With a new co-promotion agreement with Johnson & Johnson (JNJ:NYSE) forged in April, analysts say Concerta could speedily jump to a top slot in a growing $700 million market for the condition, medically known as attention deficit hyperactivity disorder, or ADHD.

And while investors punished the company for failing to complete its $7.3 billion merger with Abbott Laboratories (ABT:NYSE) last year, Alza shares have recovered this year on positive views about the launch of Concerta and the Johnson & Johnson alliance, along with other drug development advancements. The companies dropped the merger idea in January, citing antitrust concerns.

Sit Down, Billy

Although controversial, the practice of giving potent stimulants to those 3% to 5% of school kids diagnosed as clinically hyperactive isn't dissipating. For years, the drug of choice was Novartis' (NVS:NYSE ADR) **Ritalin.** But in recent years, Shire Pharmaceutical's (SHPGY:Nasdaq ADR) Adderall, an amphetamine, has claimed about half the branded market, according to IMS Health, a drug-industry market research firm.

(Chart Omitted)

ADHD is the most commonly diagnosed behavioral disorder among children, characterized by impulsivity, inappropriate attention and failure to concentrate. While experts disagree on whether the condition can be reliably diagnosed or even whether it actually exists, prescriptions for ADHD drugs have soared in the last decade, with about 1.6 million prescriptions written in April, IMS said. The drugs appear to give hyperactive kids a means for controlling their impulses.

But most hyperactivity drugs, such as SmithKline Beecham's (SBH:NYSE ADR) Dexedrine (commonly called speed) and Methylin from Mallinckrodt (MKG:NYSE), have the disadvantage of often requiring more than one dose during the day. That's created a black market for the drugs among schoolchildren who aren't diagnosed with hyperactivity. Alza's Concerta is designed to give a continuous dose of the drug for 12 hours, allowing parents to control the distribution by giving one dose in the morning. In addition, Alza formulated the pill so that it gives a strong dose in the morning, but gradually slows through the afternoon.

Special Delivery

"It's got the ideal delivery form," says Andrew Forman, a UBS Warburg analyst who has a strong buy rating on Alza; his firm doesn't underwrite for the company. "It kicks in 20 minutes and turns off in 12 hours. And it's got a far lower side-effect profile than**Ritalin.**"

Forman forecasts Concerta will generate up to $400 million in peak annual sales, depending on how much **marketing** firepower Johnson & Johnson puts behind it. And he says the drug could find other fans, such as for market pros on Wall Street, making it a possible "lifestyle" drug with off-label, or unapproved, uses. "There will be some use far beyond the pediatric market," says Forman.

Alza hopes to get Concerta on the market before the beginning of the September school year, which is likely to be more than a year before other competing products from Celgene (CELG:Nasdaq), Eli Lilly (LLY:NYSE) and Cephalon (CEPH:Nasdaq) could reach the market.

Going It Alone

Concerta, assuming it wins final FDA approval, is the latest addition to a growing Alza portfolio of drugs that the company developed on its own. Founded more than 30 years ago by biotech entrepreneur Alejandro Zaffaroni, Alza's original aim was to reformulate existing drugs for other drugmakers to make them absorb better or last longer in the body. In recent years, however, the company changed its strategy to focus on developing and selling its own drugs, a risky but potentially much more profitable market.

So far, it's paying off. Own-product revenue, which accounted for 4% of Alza revenue in 1995, generated some 40% of sales in the first quarter of 2000, and is poised to rise further. And own-product sales have been behind a 143% rise in revenue, to $796 million in 1999, from four years before, with earnings doubling in that period, before special charges.

Alza's success in selling its own products, such as Doxil for ovarian cancer and Testoderm for hormone replacement, is suddenly gaining more notice among investors. And while the stock has had a mixed performance in recent years and was particularly punished after the merger with Abbott Laboratories faltered in November, its shares have doubled from a low of 26 at the end of last year to 50 3/16 on Friday.

Alza, says Merrill Lynch analyst Steve Tighe, is "delivering on key product franchises." Merrill rates Alza an accumulate and has done underwriting for the company in recent years. "The company is firing on all cylinders," Tighe says.

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The Washington Post

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June 18, 2000, Sunday, Final Edition

SECTION: A SECTION; Pg. A01

LENGTH: 3925 words

HEADLINE: Diet Supplement Marketers Target Kids; Largely Untested Products Alarm Health Experts

BYLINE: Guy Gugliotta , Washington Post Staff Writer

BODY:

Dietary supplement companies have begun aggressively targeting children and parents as consumers of their products, among them powerful chemicals designed to help kids gain strength, lose weight or treat illnesses ranging from colds and flu to depression and even attention deficit disorder.

As a result, increasing numbers of children are swallowing supplements, often with the knowledge, urging and even insistence of parents in search of "natural" remedies or "healthy" alternatives for youngsters who eat too many cupcakes or drink too much soda. One survey recently found that almost 20 percent of parents were giving their children supplements.

In Vancouver, Wash., Nutrition Now Inc., for example, created a cuddly rhinoceros cartoon character to promote its line of dietary supplements for children, including Rhino Pops containing the herb echinacea, a cold treatment. "100% natural, Moms love the soothing support, kids love the all-natural taste, vegetarian approved," reads the legend on the box.

From Saco, Maine, Fresh Samantha Inc. ships to supermarket shelves nationwide "body zoomer" fruit smoothies that carry cartoon pictures of children to catch the eye. A 16-ounce bottle of "Oh, Happy Day" contains 100 milligrams of the herb St. John's wort "to lift the spirits." Many adults in search of an alternative to antidepressants such as Prozac take a 300-milligram tablet of St. John's wort three times a day.

Although some products may be helpful, the surge in supplement use by children and adolescents is causing rising alarm among pediatricians, children's health advocates and federal and state medical officials. At the least, many of the products may be useless. At the worst, some may be dangerous, they say. Supplements are largely untested and unregulated. The full short- and long-term impact of these substances on young bodies is virtually unknown. And in some cases, there's evidence they may be harmful.

"Physicians use medications that have been tried and tested, with known side effects," said Rossanne Philen, chief of environmental hazard epidemiology at the Centers for Disease Control and Prevention in Atlanta. "When children are given herbal preparations, they are at the mercy of the adult who is experimenting on them."

Companies offer discounts and rebates in some states to high school coaches who supply creatine, a powerful body-building nutrient, to their athletes. In Fairfax County, coaches are forbidden to promote creatine, but that doesn't stop it from being popular.

"I did a report on creatine in journalism class when I was a freshman, and I did some research on different Web sites," said Sean Curry, 16, a running back on the Chantilly High School football team who noted that he has told his parents he is using creatine. "I started taking it last year, and I'm taking it now." Curry said he has gained 31 pounds over two years. "It's definitely been valuable."

Some products even include the stimulant ephedra, which is still recommended for children by some supplement salespeople for attention deficit disorder even though it has been linked to serious illness and even death by the Food and Drug Administration. Much of the industry warns youngsters under 18 away from it.

Because there's no central source of information about adverse reactions to supplements, it is difficult to get an accurate accounting of whether they are causing widespread problems. But almost all supplements can produce some unpleasant side effects, and their overall safety remains far from clear.

The reason for this is that dietary supplements, as defined by the 1994 Dietary Supplement Health and Education Act, may be sold without pre-market clearance by the FDA or a detailed scientific evaluation of their safety and effectiveness. Also, unlike prescription drugs, the FDA must prove a supplement is dangerous before removing it from the market. As a result, thousands of products are sold over the counter to anyone who wants them--including children--with far less scrutiny than prescription drugs.

Mark Blumenthal, executive director of the American Botanical Council, an herb advocacy group, acknowledged that no one has done a "formal risk-benefit review" of dietary supplements, including those designed specifically for children. But he noted that many herbal remedies have been used for hundreds or even thousands of years and are well known outside the United States.

"With only a few exceptions, most of these herbs are some of the best-researched in the world," Blumenthal said. "In Europe, where they are sold in pharmacies, they have a stellar record of safety."

Unreported Toll

Unlike pharmaceutical firms, supplement companies are not required by law to report serious product problems to the government. Agencies rely on sporadic voluntary reports that frequently come from inexpert sources.

The American Association of Poison Control Centers, which collects data from 65 locations in all but a few states, in 1998 listed 704 reports of bad experiences with dietary supplements involving youngsters ages 6 to 18.

The association's list of supplements does not include ephedra, used primarily by adults to boost energy or lose weight and the subject of a virulent controversy between the herbal industry and the federal and state agencies seeking to regulate it.

In a report earlier this year, the FDA documented 134 cases linking serious illness--including insomnia, nervousness, seizure, hypertension, stroke and death--to ephedra during a 33-month period ending in March 1999. Ten of the reports involved children younger than 18.

In one case, a 15-year-old girl was hospitalized with severe chest pain after taking six ephedra tablets and drinking a pair of "double-shot (coffee) lattes," the FDA report said. The labeled dosage was two tablets, three times daily to lose weight, but the 125-pound victim decided to take all six pills at once.

The FDA has also documented cases of adverse effects from other supplements. Echinacea and ginseng produce minor and infrequent problems. The same is true of St. John's wort.

A substance known as DMAE, included in products marketed as alternatives to **Ritalin** for the treatment of attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD), can cause side effects similar to **Ritalin's:** insomnia, hives, headache, drowsiness and involuntary muscle movement.

Creatine, taken to enhance the body's ability to deliver energy to muscles, also causes muscles to accumulate water, which can lead to weight gain, cramping, muscle strains, dehydration, diarrhea and gastrointestinal pain. The University of Tennessee recently banned creatine after 14 of its football players had cramping episodes during one game.

Many of creatine's bad effects can be avoided by cautious use, but this is not a talent generally ascribed to the young. "High school kids don't have a clue about how to take it," said sports nutritionist Ruth Carey, a registered dietitian in Portland, Ore. "I don't find a whole lot of awareness on the part of parents, either. They don't realize it's an unstudied drug."

At the same time, there has been little research on creatine's long-term effects, and virtually none regarding its effects on young bodies.

Finally, studies have shown that the potency of many herbal supplements--including St. John's wort, ginseng and ephedra--often does not match the potency advertised on the bottle. A survey of 20 ephedra products conducted by the University of Arkansas in May found that the potency of half of them was either much greater or much less than what was indicated by the dosage listed on the bottle.

"Support for this type of thing [supplements] is simply not there. We don't know proven effectiveness. We don't know contaminants, or the concentration bottle-for-bottle," said Susan S. Baker, chairman of the American Academy of Pediatrics' committee on nutrition. "It's pretty serious. It's like taking a vial of water and not knowing whether it comes through a filter or from the sewer--and then drinking it."

Aggressive **Marketing**

Despite these misgivings, supplement companies are actively **marketing** a range of products for children using a variety of techniques.

Some strategies are obvious. Considerable science has shown that creatine increases power in short bursts in sports that require it, such as weight lifting, football and sprints.

MLO Products Co. of Fairfield, Calif., has forged a relationship with football powerhouse Mater Dei High School of Santa Ana, Calif. "How Would You Like to Increase Lean Weight By 11 lbs. In 3 Months?" read a promotion on MLO's Web site. "The Mater Dei High School football team has been consistently ranked among the top 10 teams in the country."

The company originally provided creatine to Mater Dei in order to use its athletes in a study and then publish the results, said Ryan Snyder, a sales manager. "We've just continued sponsoring Mater Dei," Snyder said. "We just want to be associated with a high-quality football program."

In Irvine, Calif., Met-Rx Engineered Nutrition has gone a step further. It has 200 high school "Mentor" programs in "almost every state," according to **marketing** directing Charlie Wright. Met-Rx supplies creatine and other supplements to athletes at 60 percent of the retail cost and sends 10 percent of the purchase price to the school's athletic programs.

Coaches and parents must approve each athlete's participation, thus opening "a communications link" about nutrition, Wright said. "Here's a way for them to get information [on supplements], save some money and create some new revenues for strengthening athletic departments."

Other **marketing** strategies simply developed from consumer demand. At Gaia Herbs, based in Brevard, N.C., herbalist Mary Bove designed a set of 20 products for children to respond to "physicians all over the states . . . calling me about giving kids herbs."

Gaia's list, one of the country's most extensive, includes products ranging from "Skin Cream for Baby Bottoms" to "Melissa Supreme for Children," an herbal treatment recommended in company literature for ADD and "impulsiveness."

Melissa, also known as lemon balm, is a medicinal tea herb and mild tranquilizer used as a sleep aid or to calm an upset stomach. Gaia's literature suggests combining Melissa Supreme with a second supplement containing St. John's wort for "hyperactivity, mood swings and tantrums."

Concern about ADD and ADHD, combined with parental misgivings about **Ritalin,** the most popular pharmaceutical treatment for these conditions, has spawned a brisk competition among companies searching for alternatives.

"Attention Focus," made by Nature's Way of Springville, Utah, uses essential fatty acids to encourage "proper transmission of brain and nerve signals," the label says. Herbs Etc., a Santa Fe, N.M., company, sells a melissa product called "Kid-A-Lin."

The Scotts Valley, Calif., company Source Naturals hit pay dirt in 1999 with "Focus Child," developed by Cathleen Rapp to find "something to appeal to people who don't want to use **Ritalin.**"

Focus Child's key ingredient, dimethylaminoethanol bitartrate or DMAE, was developed by Riker Laboratories in the 1950s and sold by prescription for nearly 30 years as "Deaner," a treatment for children's learning disabilities. But in 1983, the FDA forced DMAE's removal from the market after determining that it wasn't effective.

Nevertheless, there are several DMAE child supplements today, including chewable tablets and fruit and chocolate bars. Natural Organics of Long Island, N.Y., makes a DMAE product called "Pedi-Active A.D.D."--an "advanced diet delivery" system, according to the legend on the label.

At least one company, the Utah-based Enrich International, has promoted ephedra in the past as a substitute for **Ritalin** to treat ADD and ADHD among young children, and at least some of the company's affiliated salespeople still recommend it.

And Mary Lou Wilson, who buys Enrich products and resells them as an independent Enrich distributor based in Granbury, Tex., continues to recommend ephedra six years after she prescribed it for her grandson, Woody, then 10 and suffering from ADHD. "He used it for three months and never had to use it again," she said. "It makes such a difference."

Ephedra is a close cousin of methamphetamine, and in the past enjoyed a certain status among many young people as "legal speed" because of the kick it could give, especially when combined with other stimulants, such as caffeine.

Most large ephedra companies stopped promoting ephedra as a source of a natural high and in recent years have put labels on their products warning against the use of ephedra for any reason by anyone under 18.

But the companies' position remains ambiguous. The industry opposes a proposed New York ordinance to prohibit ephedra sales to youngsters under 18, believing "it would be more effective as a labeling issue," said Wes Siegner, counsel to the ephedra committee of the American Herbal Products Association. "You don't want to cause trouble for salesclerks."

And despite the warning labels, ephedra still enjoys considerable popularity among teenagers trying to lose weight.

Ephedra's checkered reputation makes some retailers nervous. "I won't sell the tablets to kids," said Damien Gray, branch manager for a General Nutrition Centers store a few blocks from Suitland High School in Prince George's County. "They'll take one, and it won't have any effect, so they'll take more. Who knows what's going to happen?" But the brightly colored energy-boosting ephedra drinks, many of which also carry warning labels, are a different story. "At least I know how much they're getting," he said.

Eager Consumers

Once a promotional strategy is in place, many companies are finding instant success with an eager public. The San Diego-based Nutrition Business Journal, which tracks the industry, reported 1999 sales of $ 120 million in herbal and nutritional supplements for children. In 1999,

a study conducted by National Public Radio, the Kaiser Foundation and the Kennedy School of Government found that 18 percent of parents were giving their children dietary supplements that were not vitamins or minerals.

"A lot of parents are finding that natural herbal remedies are working very effectively on their kids, and it's taking a lot of pressure off of running to the doctor every time you get a runny nose," said Amy Zanger, manager of the Crossroads Health Hut in Glendale, Ariz., near Phoenix. "People are taking charge of their own health, and the pendulum is swinging natural."

Supplement-containing "body zoomers" are "one of our top selling categories," said Fresh Samantha public relations manager Kim Mayone, who acknowledged that "Oh, Happy Day" contains "a mood-enhancing herb," but not enough for it "to be a medicine."

In less than a year, Source Nutritionals' "Focus Child" became a top-10 bestseller for a company that sells more than 400 items. For health food store manager Zanger, it was a godsend. "We're not into drugging our kids," said Zanger, worried because her son, 8, couldn't concentrate in school. "So we decided to go natural." They chose Focus Child.

"I just got his progress report card, and I almost cried; it was so much better," she added. Zanger also gives Focus Child to her 2 1/2-year-old son "before we go out to eat or to the movies" to keep him quiet. "It seems to be fine for him."

Creatine, because it works, because it's legal and because it does not appear to have any unmanageable side effects, is in a class by itself as the most popular sports nutrient on the planet, with sales of $ 400 million worldwide.

In a 1999 Blue Cross-Blue Shield Association survey, 27 percent of children ages 12 to 18 said they knew someone who used performance-enhancing substances, and more than half of those knew someone who used creatine. A survey by New York's Mount Sinai Hospital Sports Medicine Center found that children of both sexes as young as 12 were using creatine and that usage rose to 44 percent among high school seniors.

"I took it for a month to get stronger for the football season. My bench press increased 30 pounds, and my curls and squats increased 50 pounds," said Tommy McDonald, a 190-pound senior offensive guard at Jesuit High School in Portland, Ore. "All of a sudden, everything shot up very quickly. I made all-league."

But sometimes, **marketing** strategies go awry. In 1998, the ESPN sports network apologized for running a General Nutrition Centers ad for creatine during the Little League World Series.

In May, Boston's Efamol Nutraceuticals Inc. ran afoul of the Federal Trade Commission and agreed to stop advertising its products Efalex and Efalex Focus as cures for the effects of ADD and ADHD in the absence of scientific proof. J&R Research Inc. of Massena, Iowa, entered into a similar agreement for its product Pycnogenol.

Efamol was using fatty acids as key supplement components, promoting them with a slogan that said "Long Term Side Effects May Include: Hugging your Mom." J&R Research's Pycnogenol is a substance dismissed in most scientific research as showing little evidence of either safety or effectiveness.

And sometimes the bloom simply starts to fade. In recent years, there have been signs that

creatine is losing favor among those who used to be its strongest promoters--some coaches are starting to question its use. "Hell, it's not illegal, and if you want your son on it, that's your business," said Dick Adams, head football coach at Annandale High School in Fairfax County. "But I don't promote it. I tell them, 'It's a drug. Don't be frustrated with what God gave you.' "

Last year, the Texas legislature easily passed a law prohibiting public school employees from selling or promoting "performance-enhancing products" on school time after Ann Torrez complained that coaches at Hays High School outside Austin were offering to sell creatine to her son Lyndsey, then 15, to help him bulk up for the season.

"Where are they [coaches] going to be 15 or 20 years from now if this should turn out to have damaging effects?" Torrez asked at a Texas House of Representatives committee hearing. "Are they going to be there to pick up the pieces from our children? I don't think so."

That's the sentiment of Maryland health consultant Patricia Mann, the former team nutritionist for the Washington Capitals. "It's going to be years before we know what we've been doing to ourselves," Mann said. "We're not a toxic waste dump, and I don't know why people think they can put things in their body and not have bad events. You wouldn't treat your car that way."

ON THE MARKET

Dietary supplements may be sold without detailed scientific evidence of their safety and effectiveness. Thus, short- and long-term risks and benefits have not always been assessed for supplements designed specifically for children. Here are some common supplements.

* ST. JOHN'S WORT

USES: To treat depression and associated symptoms, including fatigue, appetite loss, insomnia, anxiety and nervous unrest.

SAFETY: Probably safe when for used short-term medicinal purposes. Can cause insomnia, restlessness, anxiety, irritability, fatigue, dry mouth, dizziness, headache and mania in depressed patients.

EFFECTIVENESS: Probably effective in treating mild to moderate depression, and possibly effective when used for physical symptoms associated with mild depression or to treat anxiety.

* CREATINE

USES: To increase exercise performance and muscle mass in athletes and older adults. Also used to treat heart failure.

SAFETY: Possibly safe when used appropriately, but there is insufficient infor-mation on safety

of long-term use. Can cause nausea and diarrhea. Athletes report muscle cramping.

EFFECTIVENESS: Possibly effective when used to enhance muscle performance during brief, high- intensity exercise. Likely ineffective when used for increasing endurance.

* ECHINACEA

USES: For treating or preventing colds and other upper respiratory infections. Also as an antiseptic, antiviral and immune stimulant, dilator of blood vessels and treatment for urinary infections.

SAFETY: Likely safe when daily use is limited. There is concern that long-term use might depress immunity. Can cause allergic reactions, including acute asthma and hives.

EFFECTIVENESS: Possibly effective as therapy for influenza-like infections, or for shortening the duration of colds and as supportive treatment for respiratory infections.

* DMAE or Dimethylaminoethanol

USES: For treating attention deficit disorder, enhancing memory and mood, boosting cognitive function, increasing physical energy and improving athletic performance.

SAFETY: Possibly safe when used appropriately. Can cause constipation, hives, headache, drowsiness, insomnia, confusion, depression, elevated blood pressure and mania.

EFFECTIVENESS: Possibly effective in combination with other supplements in improving exercise performance. Clinical studies of use in treating attention deficit disorder have been inconclusive.

* GINKGO BILOBA

USES: To treat cerebral conditions and to increase alertness. Also used to improve cognitive function and sleep in depressed patients.

SAFETY: Likely safe when used appropriately, unsafe when used intravenously. May cause gastrointestinal pain. Large doses may cause restlessness, diarrhea, nausea and vomiting.

EFFECTIVENESS: Possibly effective when used to stabilize or improve cognitive function in patients with cerebral conditions, or when used to treat dizziness and headache.

* EPHEDRA, also known as ma huang

USES: For asthma, bronchitis and allergic disorders, and as a stimulant and appetite

suppressant. Used for weight loss in combination with other herbal products.

SAFETY: Possibly safe when used short-term. Likely unsafe in high doses or long-term. Can cause dependence. Adverse reactions include anxiety, insomnia, high blood pressure and heart failure.

EFFECTIVENESS: Effective in short-term treatment of diseases of the respiratory tract. Likely ineffective when taken as a single agent for weight loss. Insufficient reliable information about other uses.

* VALERIAN

USES: As a sedative and for mood disorders such as depression, infantile convulsions, epilepsy and attention deficit hyperactivity disorder.

SAFETY: Possibly unsafe when used long-term or in high doses. Can cause headache, excitability, uneasiness, cardiac disturbance and insomnia and, occasionally, morning drowsiness.

EFFECTIVENESS: Possibly effective when used for improving sleep quality and for improving mood and concentration.

* MELISSA (lemon balm)

USES: As a digestive, mild tranquilizer and for stimulating appetite. Traditionally used to promote sweating and to treat nervous problems, insomnia, cramps, headache and toothache.

SAFETY: Possibly safe when used on a short-term basis -- no more than 14 days. Hypersensitivity reactions have been reported.

EFFECTIVENESS: Possibly effective when used for nervous sleeping disorders and gastrointestinal pain or as topical treatment of cold sores.

SOURCE: Natural Medicines Comprehensive Database

More information about supplements is available at the following World Wide Web sites: Nutritionalsupplements.com, NutritionNewsFocus.com, Vicus.com, Vitacost.com.

GRAPHIC: IG,,SETH HAMBLIN & TOBEY

The Associated Press

View Related Topics

August 1, 2000, Tuesday, BC cycle

SECTION: Business News; Washington Dateline

LENGTH: 494 words

HEADLINE: FDA approves single-dose form of attention-deficit drug

BYLINE: By RANDOLPH E. SCHMID, Associated Press Writer

DATELINE: WASHINGTON

BODY:

The first single-dose form of the drug most widely used to treat attention deficit disorder in children won government approval Tuesday.

The Food and Drug Administration said it had approved Concerta for the treatment of attention deficit hyperactivity disorder.

Between 4 percent and 12 percent of school-age children - an average of about 2.5 million, mostly boys - are believed to have ADHD. Symptoms include short attention span, impulsive behavior and difficulty focusing and sitting still.

Methylphenidate - best known under the name **Ritalin** - often is prescribed to increase a child's alertness.

But current forms of the drug require two or three doses daily, often requiring youngsters to break up their schooldays with visits to the nurse's office.

The new drug lasts 12 hours, which will avoid in-school and after-school dosing.

Concerta was developed by Crescendo Pharmaceuticals Corp. and will be manufactured and marketed by ALZA Corp. of Mountain View, Calif.

The new form of the drug will eliminate the stigma of taking a drug in school and the problems of getting it to the school nurse or interrupting after-school programs or practice, said Dan Swisher, vice president of ALZA.

"It makes the condition private. It eliminates the embarrassment for children," he said in a telephone interview.

Swisher said McNeill Consumer Healthcare is assisting in the **marketing** of Concerta, which should be available in two weeks. He said the price has not been determined but will be comparable to other ADHD treatments.

Typically, people suffering from ADHD have problems following instructions and paying attention. They may seem not to listen; be disorganized; miss details; have trouble starting tasks, or performing tasks that require planning or long-term effort; appear to be easily distracted or forgetful. In many cases they seem "hyper," being fidgety, impulsive and unable to wait their turn.

Not all people with the disorder exhibit all the symptoms all the time.

Many of the symptoms also are associated with youthful rambunctiousness, which has raised questions whether today's youngsters are being overdiagnosed and overdrugged.

As a result, the American Academy of Pediatrics issued in May its first guidelines for ADHD, hoping to eliminate incorrect diagnoses and ensure untreated children get the help they need.

The guidelines are for children 6 through 12. Most ADHD research has involved that age group.

Concerta is an extended-release formula in tablet form designed to be taken in the morning before a child leaves for school.

In clinical trials the most common side effects were headaches, reported by 14 percent of patients. Less common were upper respiratory tract infection and stomachache.

On the Net: Food and Drug Administration: http://www.fda.gov

American Academy of Pediatrics: http://www.aap.org

National Attention Deficit Disorders: http://www.add.org/content/abc/basic.htm

LANGUAGE: ENGLISH

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CBS News Transcripts

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SHOW: CBS EVENING NEWS (6:00 PM ET)

July 16, 2000, Sunday

TYPE: Newscast

LENGTH: 672 words

HEADLINE: DOCTORS CAUTIONING PARENTS TO BE CAREFUL WHEN USING UNPROVEN HERBAL REMEDIES ON CHILDREN

ANCHORS: SHARYL ATTKISSON

BODY:
SHARYL ATTKISSON, anchor:

For many parents, the idea of treating childhood ailments with natural remedies is an appealing one. But does the fact that a product is natural automatically mean that it is safe? The concerns over herbal remedies for children are the focus of tonight's Weekend Perspective.

For Janet Mandell, it all started with a cry in the night.

Ms. JANET MANDELL (Herbal Remedy User): When she was about 18 months old, when she had a raging ear infection, she had a really high fever. Her fever was nearly 105. And I was kind of a new mother. She was 18 months. I was scared. I went to the MD, pediatrician. He looked in her ears and he said, 'Whoa, this really needs antibiotics.'

ATTKISSON: But Mandell was nervous about giving antibiotics to a child so young, so she decided to give Lily an herbal remedy.

Ms. MANDELL: And when she went back to the pediatrician 10 days or two weeks later, he looked in her ears and everything was fine.

ATTKISSON: She isn't alone. A recent survey found 20 percent of American parents are using supplements for their children's runny noses, fevers and even attention deficit disorder. And manufacturers hope to increase that number by **marketing** herbal combinations formulated especially for children.

Mr. DANIEL GAGNON (President, Herbs Etc.): Parents are looking for something that's safer for their children and will do what their body--will do a better job with their body.

Reishi mushroom is one of the absolute best to help tonify your immune system.

ATTKISSON: Daniel Gagnon's company, Herbs Etc., makes a product called kidalin, sort of an herbal **Ritalin.**

Mr. GAGNON: Parents would come in and say, 'I need something to keep my child calm.' So I started playing with different formulations, putting them together, and then testing it in the store over and over and over until we found a formulation that was effective.

Dr. ROSSANNE PHILEN (Centers for Disease Control): The problem, of course, with most of these supplement products is they haven't been tested in adults, much less in children. So we don't know if they're potentially beneficial or potentially very harmful. And we especially don't know that for children.

ATTKISSON: Dr. Rossanne Philen of the Centers for Disease Control fears parents may believe that because supplements come from natural products, they're safer than pharmaceuticals.

Dr. PHILEN: Certainly there are a lot of natural products that we're all familiar with which are not sa--safe. One good example is snake venom, for instance. No one would argue that poison ivy is safe.

ATTKISSON: Unlike drugmakers, supplement companies aren't required to report adverse reactions, but in 1998 alone, poison control centers recorded more than 5,000 incidents involving children under 18. Doctors are especially concerned about the stimulant ephedra. Marketed as a way to boost energy and lose weight, ephedra has become popular with teen-agers, who see it as legal speed.

Ms. KAREN SCHLENDORF (Mother of Ephedra Victim): How could my healthy, wonderful, gorgeous son have died from something he bought in a T-shirt shop?

ATTKISSON: Karen Schlendorf's son died in 1996 after taking ephedra.

Ms. SCHLENDORF: Pete was the 16th person that died from taking these over-the-counter herbal supplements, and our family vowed that we would do everything we could to be sure that there wasn't a 17th. Well, there has been a 17th and an 18th and a 19th and a 20th.

ATTKISSON: Pete's parents have spent the last four years fighting for laws to prevent anyone under 18 from buying ephedra products.

Ms. SCHLENDORF: There are herbal supplements that are OK, you know, and I'm not going to sit here and tell people you should never take any of them. But are you willing to have your children take the same risk?

ATTKISSON: As matters stand now, a dietary supplement can be removed from the market only if the Food and Drug Administration can prove it is dangerous.

(Announcements)

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September 12, 2000, Tuesday, Final Edition

SECTION: HEALTH; Pg. Z34

LENGTH: 1413 words

HEADLINE: TREATMENT OF CHOICE; ADHD: Too Many Diagnoses? Too Few? Both?

BYLINE: Kathleen F. Phalen , Special to The Washington Post

BODY:

Q: My 4-year-old son started preschool recently and his teacher says he's been acting out and can't stay in his seat. A friend suggested he might have ADHD. Can you tell me more about it?

A: It's a common sight: the kid who is driving his parents crazy, unable to follow through on even the simplest request. His teachers say he can't wait his turn, blurting out answers or bullying his classmates. His relationships are suffering and he's starting to believe he's bad.

While many children occasionally fit this description, for those with attention deficit hyperactivity disorder (ADHD), it's a chronic condition that can have widespread effects. Although researchers do not know what causes ADHD, studies suggest it is a disorder of the central nervous system that can be inherited.

Children with ADHD often have higher than average injury rates, due to acting before thinking; school can be more difficult for them because they cannot pay attention or complete tasks; peers may reject their aggressive advances; and many are depressed as a result of continuing negative attention.

According to a consensus conference convened by the National Institutes of Health (NIH) in 1998, ADHD is the most commonly diagnosed behavioral disorder of childhood, estimated to affect 3 to 5 percent of school-age children. Boys are three times as likely as girls to be diagnosed with the disorder, whose symptoms include inappropriate levels of attention, concentration, activity, distractibility and impulsivity.

The consensus statement cites variations in diagnosis and treatment among practitioners: "Data indicate that family practitioners diagnose more quickly and prescribe medication more frequently than psychiatrists or pediatricians." The quick diagnosis can be attributed to several factors, says Ann Abramowitz, who heads the Center for Learning and Attention Deficit Disorders at the Emory University School of Medicine in Atlanta, including a lack of time spent with the patient and family. "They may be inattentive or hyperactive, but we have to find out

why," she says. There could be other things going on in a child's life--not enough sleep, nutrition problems, seasonal allergies, family crisis or unstructured home environment--that may be causing symptoms and behaviors that are typical of ADHD--or of something completely different.

While there's concern that many children are wrongly being diagnosed with ADHD, Peter S. Jensen, director of Columbia University's Center for Advancement of Children's Mental Health in New York, says about half of those who actually have the illness are not getting help. "This is one of the biggest health hazards," he says. "Even with all the [media] attention, a substantial number are still being missed."

As he explains it, an ADHD child who is inattentive but not hyperactive may get labeled as unmotivated, lazy or learning disabled. Girls with ADHD tend to get missed more than boys because they show less of the hyperactive behavior.

A study of Maryland children published in the September issue of the Journal of Pediatrics found that whites were much more likely than others to be taking **Ritalin,** one of the prescription drugs used to treat ADHD; black students had the lowest rate of use. "African Americans, Latinos, Asians get missed," Jensen says.

Paul H. Wender, a psychiatrist who conducted some of the first clinical trials on **Ritalin,** says it takes more than a 15-minute HMO visit to tell the difference between normal childhood behavior and ADHD. "It requires several hours with parents," says Wender, who practices in Andover, Mass. "You can't just write prescriptions."

Common Treatment Options

When ADHD is suspected, parents should consult a licensed practitioner familiar with the disorder, since self-prescribing with either traditional or alternative therapies could be dangerous.

Prescription drugs commonly used for ADHD are **Ritalin** and Adderall (dexedrine). While some parents fear these stimulants could lead to addiction and abuse, Jensen says there's a greater risk of drug abuse in adolescence if ADHD is not treated. "Ninety percent of data suggests that if we treat with medications now, we lower later substance abuse problems," he says.

Manufacturers are making these drugs more convenient to use. "The newer Adderall lasts longer," Jensen says, and Concerta, a timed-release form of **Ritalin's** active ingredient, methylphenidate, "gives true once-a-day dosing."

Many practitioners prefer multimodal therapies, combining drugs with behavioral strategies to help keep ADHD's symptoms under control.

Abramowitz says it can be very effective for families to establish clear rules, a high degree of structure in daily life and consequences for misbehavior. "There needs to be a defined place to

put schoolwork when done; where does the student find work; what do they do when finished; break the day into clear time segments, and have the child get a brief behavior rating for each segment," she says.

Alternative Approaches

A recent investigation by The Washington Post revealed widespread **marketing** of dietary supplements to children, with some products being portrayed as nondrug options for treating ADHD. Public health officials consider this approach risky, since dietary supplements are largely unregulated and potentially hazardous.

Nonetheless, with many parents afraid of endangering their children with powerful drugs, they often consider alternative medicine. Among the treatments offered by practitioners in that field are meditation, biofeedback and herbs such as lemongrass and chamomile.

"**Ritalin** treats the symptoms," says Rockville medical acupuncturist Nader Soliman, who is also an anesthesiologist at Shady Grove Hospital. "With acupuncture, it is a method of normalizing the body energetics, and I have treated adults and children with no recurrence of symptoms."

With a small probe aimed at acupuncture points in the ear, he says he is able to pick up areas of electrical disturbance. "If there is an electrical variation," he says, "then we stimulate the area to restore it to normal function," using "microcurrent electrostimulation" instead of traditional acupuncture needles. He also uses homeopathic remedies.

Chris Meletis, chief medical officer at the National College of Naturopathic Medicine in Portland, Ore., says a recent study linked ADHD to sleep deprivation due to enlarged tonsils. In addition to considering dietary changes--he urges patients to avoid caffeine, peanuts, citrus, dairy and additives--he looks for a shortage of essential fatty acids and for deficiencies of such minerals as zinc and chromium.

According to Rick Cantrell, a pastoral psychologist and homeopathic physician in Asheville, N.C., "symptoms of ADHD are usually related to nutrition, hypoglycemia being the number one cause. . . . Ninety percent of the time, the child is suffering from hypoglycemia or allergies to chemicals, dyes or pesticides. When these causes are eliminated, the symptoms of ADHD go away."

Also claiming to have "a safe, effective alternative to **Ritalin,**" Jeanette Farmer, a certified handwriting remediation specialist in Denver, has students perform handwriting movements that she likens to the old Palmer method of penmanship exercises. "These movements hone and stabilize the brain," she says. She cites her own research and European studies that connect these exercises with improving a child's emotional state, behavior, attentiveness in school, ability to learn and ability to get along with others.

RESOURCES

* National Attention Deficit Disorder Association:

1788 Second Street, Suite 200, Highland Park, IL 60035

847-432-ADDA; www.add.org.

* National Institute of Mental Health:

6001 Executive Boulevard, Rm. 8184, MSC 9663, Bethesda, MD 20892-9663

301-443-4513;www.nimh.nih.gov.

* Children and Adults with Attention-Deficit Hyperactivity Disorder (CHADD):

8181 Professional Place, Suite 201, Landover, MD 20785

800-233-4050 or 301-306-7070; www.chadd.org.

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October 3, 2000, Tuesday

SECTION: LIFESTYLE

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BYLINE: By Emily Sohn

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But the government has not approved its use in kids. And nobody has looked at the drug's long-term effects on the still-developing brain.

New research on members of Generation Y and their successors is under way, though. For the first time, scientists are gathering extensive data to better diagnose childhood depression and decide what to do about it. "This is a new frontier with children and adolescents," said pediatrician Jerry Rushton.

Exploring depression in young people is tough to do. Diagnosing the disorder in children isn't easy, and kids don't respond to drugs the same way adults do. A few small studies suggest that medications may help depressed kids. Longer-term research may show that combining medications with non-drug therapies will work even better.

Prozac hit the U.S. market as an antidepressant for grown-ups in 1987. It was the first of a family of drugs that increase levels of a chemical called serotonin in the brain. Some brain cells ordinarily produce the chemical, which carries messages between cells influencing mood, sleep and aggression, among other things. Because they prevent cells from absorbing serotonin, drugs like Prozac are called selective serotonin reuptake inhibitors, or SSRIs.

Prozac, along with cousins Paxil and Zoloft, among others, have been studied extensively in adults and animals. But research on children has begun only in the last several years.

That hasn't stopped doctors from prescribing the drugs to their young patients.

In a survey of 600 doctors in North Carolina, Rushton, of the University of Michigan, found that 72 percent had prescribed a serotonin-influencing drug to a patient younger than 18. His results appeared in the journal Pediatrics in June.

Such statistics worry many doctors. "You can't treat children as mini-adults," said Joan Luby, a child

psychologist at the Washington University School of Medicine in St. Louis. For any medication, dosage must be tailored carefully, taking into account the child's stage of development, she said.

One reason antidepressant studies in children have lagged behind adult studies is that people have only recently begun to accept that children can suffer from depression, anxiety disorders and other mental illnesses.

"We thought we could be touchy and feely and nice, and every kid would get better," said Peter Jensen, director of the Center for the Advancement of Children's Mental Health at Columbia University in New York.

In fact, depression can strike children just as severely as it does adults, and tough times are not necessarily a normal part of growing up. Studies show that more than 8 percent of children in the 7- to 18-year-old age group suffer from depressive disorders, about as often as the same illnesses show up in adults. Mood disorders, more than anything else, put adolescents at risk for suicide, the third-leading cause of death for people between 15 and 24. Strong evidence also suggests that depressed children are likely to become depressed adults, with a relapse rate as high as 70 percent. And depression tends to run in families.

Yet, discovering depression's symptoms in young people is enormously difficult. Adults can take themselves to a therapist if they're feeling low. But children rarely recognize their own mental illnesses. Some depressed children seem quiet or antisocial and get lost in the shadows of their boisterous peers. In other cases, depression causes behavioral problems, which are more likely to earn punishment than sympathy. Kids with mental illnesses "are over-represented in the juvenile system, under-represented in mental health institutions," said Graham Emslie, a child psychiatrist at the University of Texas Southwestern Medical Center at Dallas.

Depression also often appears alongside other problems, such as anxiety disorders, behavior disorders, learning disabilities and substance abuse.

Even doctors have trouble recognizing the symptoms of childhood depression, mostly because they've never learned how to do it, Jensen said. In a study this year, he found that only half of the 200 pediatricians surveyed felt confident in their ability to diagnose and treat depression in kids. Three-fourths thought they could use more information for treating the illness in young people. That's out of line with his finding that 66 percent of the 300 parents surveyed thought that their primary-care physician knew how to recognize and treat childhood depression.

"Doctors are saying, 'No we don't. We don't know enough about it,'" Jensen said.

Some better-studied illnesses have helped researchers tackle the unknowns of childhood depression, however. For example, researchers set out guidelines for diagnosing and treating attention-deficit/hyperactivity disorder, or ADHD, decades ago.

A group led by Emslie has been working to do the same for depression. In a conference in Dallas in 1998, he helped create a step-by-step guide for doctors to spot childhood depression and pick the right kind of treatment. The results appeared in the Journal of the American Academy of Child and Adolescent Psychiatry at the end of last year. Luby will soon publish results of a similar effort for preschoolers.

Refining guidelines depends on research, though, a point made clear by a major ADHD study published in the journal Archives of General Psychiatry last December. The 14-month study of almost 600 children found that in most cases, the stimulant **Ritalin** helped reduce the symptoms of ADHD in kids between 7

and 10 years old. The drug was more effective than intensive behavioral therapy, and the combination of medication and non-drug therapies didn't help much more than the medication alone.

Prozac is a different kind of drug from **Ritalin,** but researchers are using the design of long-term **Ritalin** studies as a guide for studying Prozac, said Jensen, one of the ADHD study's authors. Doctors also take clues from adult studies, which show that Prozac-like drugs work better than the old generation of antidepressants, with far fewer nasty side effects.

The first studies on children suggest that the same may be true for young people, and not just for depression.

Benedetto Vitiello, of the National Institute of Mental Health in Bethesda, Md., had overwhelming success treating anxiety disorders with fluvoxamine, the chemical name for Luvox, one of Prozac's cousins. Seventy-six percent of the children in his three-week study who took the drug improved, compared with 29 percent of those taking a placebo. He presented his results at a meeting of the New Clinical Drug Evaluation Unit in Boca Raton, Fla., this spring.

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Still, experts advise caution. No studies have looked at the drug's long-term effects in children. Antidepressant drugs target the brain, which rewires itself in important ways during a child's development. Animal studies suggest that rats treated before birth with serotonin-influencing drugs carry long-term brain abnormalities into adulthood.

In young children especially, when the brain is learning how to see, talk, and perfect motor skills, the consequences could be greatest. "I advise extreme caution with drugs not appropriately studied," Luby said. "Prozac is definitely in that category."

Caution should not preclude drug treatment, however. "We all worry," Jensen said. "We'd be crazy not to worry." But worry can be counterproductive when a child's mental wellness is at stake, he said. "We have to worry about parents' worries getting in the way of rational decision-making for their child."

Not treating depression could be riskier than treating with medications, many doctors warn. "I tell parents what I would do if it were my child," Jensen said. "We know these disorders themselves affect brain development. Those medications could also have effects on the brain. They could be positive, wiring new programs saying, 'We could go somewhere in life.'"

Studies have shown that abused monkeys, for example, have brain abnormalities the rest of their lives. Drugs might be able to reverse that damage and prevent relapses. "Taking drugs while the brain is developing could have a positive effect, because the illness would have a negative effect," Emslie said. For all age groups, he thinks antidepressants are under-prescribed, not over-prescribed, and estimates that only

between 10 and 20 percent of depressed people have sought treatment.

Like any other illness or disease, depression must be taken seriously. "There is a lot of misunderstanding that medications are bad," Jensen said. "They're certainly not bad if you have cancer and need cancer medication. They're certainly not bad if you have seizures and need seizure medication." A diabetic wouldn't forgo insulin for a few weeks, Emslie said. Most people with bacterial infections don't hesitate to take antibiotics.

Depression differs from other illnesses in important ways, though, and few experts suggest that drugs alone can conquer it. Certain kinds of non-drug therapy have been helpful in treating childhood depression. One particularly type, called cognitive behavioral therapy, involves identifying depression-causing thought patterns and changing them. In the Journal of the American Academy of Child and Adolescent Psychiatry in 1995, researchers reported a 60 percent remission rate for depressed kids treated with cognitive behavioral therapy, compared with less than 40 percent remission for two other kinds of non-drug therapy.

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The upcoming expiration of the Prozac patent may also fuel more kid research. The patent is set to expire as soon as next February, but Eli Lilly and Co., the producers of Prozac, can earn a six-month patent extension if they test the drug on children. Six months can mean a lot of money for a drug like Prozac, Emslie pointed out. "There's obviously a long list of generic companies waiting to make depression drugs," he said.

But the new regulations have unleashed another concern. Some wonder what the consequences will be when FDA-approved labels allow drug companies to start **marketing** Prozac and other antidepressants for use in children. "How do parents and physicians deal with ads saying, 'Is your child depressed?'" wonders Rushton of the University of Michigan.

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