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Developing a Novel Surveillance Method to Identify the Rates of Idiosyncratic Adverse Drug Reaction, Pemoline as a model.

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ABSTRACT AND KEYWORDS

Background: Pemoline was introduced in 1975 in the U.S. for ADHD in children. Pemoline was withdrawn from the market 30 years later, due to fatal hepatotoxicity associated with its use.

Objective: To create a system that will estimate the potential association between a serious adverse event and a medication early in its marketing cycle.

Method: All cases of acute liver failure (ALF) associated with pemoline reported to the FDA and all published articles on topic were reviewed. The incidence rate of idiopathic ALF was synthesized from the published literature. The data were analysed by using the Fisher Exact test and Relative Risks (RR).

Results: As early as 1978, there was a significant signal indicating that pemoline is associated with ALF.

Conclusion: This method enables researchers, drug companies and regulators to identify uncommon adverse drug reactions, caused mostly by new medications, earlier in the course of marketing and thus prevent serious human risk.

Key words: Pemoline, Adverse Drug Reactions, Idiosyncratic, Acute Liver Failure, Postmarketing Surveillance, Attention Deficit Hyperactivity Disorder, Food and Drug Administration.

Dedication

This thesis is dedicated to my parents, Professor Abdurahman Tawil and Hamida Elbanani, for their unconditional love and invaluable support.

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TABLE OF CONTENTS

CERTIFICATE OF EXAMINATION ii

ABSTRACT AND KEYWORDS iii

DEDICATION v

ACKNOWLDGEMENTS vi

TABLE OF CONTENTS vii

LIST OF TABLES ix

LIST OF FIGURES xi

LIST OF ABBREVIATIONS xiii

CHAPTER ONE: INTRODUCTION 1

1.1 Statement of the Problem 1

1.2 Significance and Rationale 2

1.3 Pemoline-Relevant History and Index Case 6

1.4 Overview of pemoline 9

1.5 Literature Review of Pemoline Induced Hepatotoxicity 20

CHAPTER TWO: HYPOTHESIS & OBJECTIVES 25

CHAPTER THREE: METHODS 26

3.1 Research Questions 26

3.2 Study Design 27

3.3 Data Collection 30

3.4 Data Analysis 35

CHAPTER FOUR: RESULTS 37

4.1 The Rate of Idiopathic Acute Liver Failure in Children 37

4.2 The Yearly Number of Children Taking Pemoline in the U.S. 39

4.3 The Yearly Number of Children Taking Pemoline in Canada 42

4.4 The Annual Number of Children on Pemoline in the US and Canada Who Developed ALF 46

4.5 The Data Analysis of Children on Pemoline Developing ALF from 1977 to 1993 53

CHAPTER FIVE: DISCUSSION 60

5.1 Discussion of Findings 60

5.2 Study Limitation 70

5.3 Implications of the Study for Clinical Practice 72

5.4 Future Research Directions 73

CHAPTER SIX: CONCLUSION 74

REFERENCES 75

CURRICULUM VITAE 82

LIST OF TABLES

Table (1): The pemoline strengths, trade names, product imaging and their manufacturing companies. 11

Table (2): Naranjo ADRs probability scale criteria. 33

Table (3): Naranjo ADRs probability classification. 34

Table (4): Medical literature reports of percentage of idiopathic ALF in children. 38

Table (5): Literature reports of U.S. school children on ADHD medication and on pemoline therapy from 1975 to 1993. 40

Table (6): The calculated number of children on pemoline in the U.S. per year. 41

Table (7): The calculated number of children on pemoline for each year in Canada from 1987 to 2004. 44

Table (8): Clinical details of 30 FDA cases with pemoline-induced hepatotoxicity from 1975 to 1998. 48

Table (9): Medical literature reports of ALF and hepatic death ascribed to pemoline. 50

Table (10): Naranjo causality assessment scores of the medical literature reports of ALF ascribed to pemoline. 52

Table (11): The yearly Relative Risk and 95% confidence intervals of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports). 56

Table (12): P-values from the Fisher exact test of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports). 58

Table (13): Relative Risks and P-values of children on pemoline developing ALF from 1977 to 1993 (cases from the literature reports). 59

LIST OF FIGURES

Figure (1): The chemical structure of pemoline. 10

Figure (2): Sites of action of pemoline on the release and reuptake of dopamine at sympathetic neuroeffector junctions. 15

Figure (3): Design of the research study. 29

Figure (4): Cumulative chart of children taking pemoline for an entire year from 1987 to 2004 in Canada. 45

Figure (5): Cumulative chart of children developing ALF after taking pemoline and children on pemoline, from 1975 to 1993 in U.S. and Canada. 49

Figure (6): Cumulative chart of children developing ALF after taking pemoline from 1975 to 1998 (the cases are from the FDA and from the medical literature). 51

Figure (7): Relative Risks of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports). 55

Figure (8): P-values from the Fisher exact test of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports). 57

Figure (9): Number of children taking pemoline from 1987 to 2004 in Canada. 64

Figure (10): P-values from the fisher exact test of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports and from literature reports). 69

LIST OF ABBREVIATIONS

Adverse Drug Reactions	ADRs
United States	U.S.
Food and Drug Administration	FDA
Attention Deficit Hyperactivity Disorder	ADHD
Acute Liver Failure	ALF
Relative Risk	RR
Confidence Intervals	CIs

CHAPTER ONE: INTRODUCTION

1.1 Statement of the Problem:

It typically takes many years before an association of a drug with a rare adverse reaction is established. To enhance patient safety, there is a need to develop robust and rapid methods to identify such associations in as timely a manner as possible.

1.2 Significance and Rationale:

With the use of any pharmaceutical product comes the risk of unintended adverse events. These events include adverse drug reactions (ADRs) (Lortie, 1986). Adverse drug reactions represent an important clinical issue. Each year prescription drugs cause fatal ADRs to 100 000 people in the United States (U.S.), making prescription drugs between the fourth and sixth leading cause of death, after heart disease, cancer, stroke, pulmonary disease, and accidents (Lazarou et al., 1998). The picture in Canada is slightly different; a Canadian study stated that approximately 1824 deaths occur annually due to ADRs in Canada, causing ADRs to be the 19th leading cause of death (Bains & Hunter, 1999).This is a lower rate than the above U.S. study. Despite their different rates, the above two studies highlight the seriousness of ADRs, making ADRs a major public health issue.

Before a pharmaceutical product is marketed, the manufacturer must prove that it is both effective and safe by performing extensive studies in animals and in human clinical trials. However, premarketing studies cannot guarantee product safety. Such studies are limited by the small numbers of

patients in pre-marketing clinical trials (between 1,000 and 3,000 patients) which reduces the chance of finding rare adverse effects. Importantly, typical serious ADRs (e.g. agranulocytosis) often occur at a rate of between 1:1000 and 1:10,000 patients. Additionally, the subjects included in the clinical trial usually do not include vulnerable populations such as pregnant women, children, elderly people, those with complicated diseases, or those taking other medications. Hence, uncommon side effects, delayed effects, or consequences of long-term drug administration often are not observed before the drug has been marketed (Stricker & Psaty, 2004). Typically, at the time of licensing, only 1,000-3,000 patients will have been exposed to the drug. This provides very limited statistical power to detect rare but serious adverse drug reactions. The more common type A ADRs (reactions that are an augmentation of the normal pharmacological actions of the drug) may already have been identified by the time of licensing (Pirmohamed et al., 1998). By contrast, type B ADRs (idiosyncratic or bizarre reactions that cannot be predicted from the known pharmacology of the drug), which are relatively uncommon, will only be detected after licensing through postmarketing surveillance (Meyboom et al., 1997). A study with power of 0.95 to detect an adverse event requires at least 30,000 people to be treated with a drug to discover at least one patient with an adverse reaction which

has an incidence of 1 in 10,000 (B. H. C. Stricker, 1992). Such adverse effects, once recognized, may be serious enough to result in the withdrawal of a drug; examples include agents that produce hepatotoxicity such as bromfenac and troglitazone (Lee, 2003).

Postmarketing studies are based on collecting spontaneous case reporting of ADRs. Case reports are among the most important tools for observational research (Vandenbroucke, 2001). There are two systems where clinical observers can be used to address their voluntary reporting of ADRs. The first is the published medical literature, which is a highly efficient warning system for new adverse reactions, and often recognizes rare events and people at high risk (Begaud et al., 1994). The second consists of national and international adverse drug reaction monitoring centers, such as the Food and Drug Administration (FDA). In the U.S. the FDA started a voluntary reporting system in the late 1960s. The FDA gets reports from health care providers, consumers and pharmaceutical companies. Unlike health care providers and consumers, the manufacturers have a regulated duty to report to the FDA on any ADR. The system had been criticized in the 1970s for its delay in sending reports of the newly identified ADRs to the Physicians Desk Reference (Lortie, 1986). The FDA system is probably overwhelmed by ADR reports from all interested parties,

as the experts at the Agency have insufficient time to analyze all incoming reports in depth. Moreover, the FDA does not have the regulated authority to mandate drug manufacturing companies to conduct directed postmarketing surveillance studies (Zielinski, 2005), which could help in detecting uncommon serious ADRs.

Postmarketing studies have to be conducted shortly after the new drug is marketed and its use becomes widespread in the population. The large number of patients using the drug then creates a good opportunity to detect uncommon idiosyncratic adverse drug reactions. Once a few cases of serious ADRs that may lead to organ failure are reported to the FDA, it is possible that a novel detection method could allow the Agency to create a rapid signal for an association between the drug and the corresponding ADRs. This method would allow the FDA and manufacturers early identification of any rise in the incidence rate of unknown severe organ failure associated with the medication. Thus, this method would serve to protect the public from unexpected harmful effects of new drugs. In this thesis we have used pemoline-associated acute liver failure (ALF) as a model for development of a novel system to detect serious unpredicted ADRs.

1.3 Pemoline-Relevant History and Index Case:

Pemoline (phenylisohydantoin, Cylert™) is a mild central nervous system stimulant that has been used principally in children with behavioral disorders. It has proven effectiveness in children with attention deficit hyperactivity disorder (ADHD) (Millichap, 1976; Stevenson & Wolraich, 1989) (See section 1.4 Overview of pemoline). Pemoline was approved by the FDA for the treatment of ADHD on January 27, 1975. From 1975 to 1995, it was not appreciated that pemoline can cause acute liver failure (ALF). In 1995, a group from the Hospital for Sick Children, in Toronto Canada, reported a case of a 14-year-old boy diagnosed with ADHD (Berkovitch et al., 1995), who was previously healthy and received concomitant pemoline, 37.5 mg a day, for 16 months and methylphenidate, 20 mg a day for 2 months, to control his behavioral problem. He was hospitalized due to jaundice, which progressed into acute liver failure. A liver biopsy was suggestive of drug toxicity. He needed a liver transplant, but unfortunately the liver transplant failed and the child died. All known causes of liver failure were ruled out like infection, metabolic disease, tumor, or chemicals. At that time the medical community had no appreciation that pemoline or methylphenidate could cause liver failure. The

physicians caring for the child referenced the relevant literature and found two previous published fatal cases due to ALF where pemoline was the agent suspected of causing the ADR (Jaffe, 1989; Nehra et al., 1990); both cases were from the U.S. Berkovitch and colleagues wrote that, "the U.S., FDA, and the manufacturer are not aware of additional cases". They calculated that a child receiving pemoline has a relative risk of development of liver failure of 45.3 (95% confidence interval, 4.1 to 510). This highly significant association ($p < 0.001$) suggests causation. After this report, other investigators around the world reported more cases of liver failure due to pemoline (See section 1.5 Literature Review of Pemoline Induced Hepatotoxicity). A black box warning was added to the labeling in the United States in December 1996, and a "Dear Doctor" letter was mailed out from Abbott to all U.S. physicians to use the drug as a last resort, but medical doctors continued to use pemoline as a first line therapy (Will et al., 2002). In Sep. 1999, Health Canada withdrew pemoline from the Canadian market (Hogan, 2000). More pemoline liver toxicity cases appeared, and there was pressure on the FDA to ban the drug. In May, 2005, Abbott chose to stop sales and marketing of Cylert™ in the U.S. Cylert™ will remain available through pharmacies and wholesalers until supplies are exhausted; no additional product will be available. In November 2005 pemoline was

finally removed from the U.S. market (Pemoline removed from US market.2005).

From the story of pemoline one can note that there appears to be an entire generation in delay in identifying pemoline-associated ALF, leading to a delay in withdrawing the drug from the market and as a consequence, putting children at risk for serious drug-related injury and death. In this thesis we present a new method that could have allowed detection of this serious ADR less than 4 years after the introduction of the drug into the U.S. market.

1.4 Overview of Pemoline:

1.4.1 Pemoline Description:

Pemoline is a mild central nervous system stimulant, which although structurally different from amphetamine and methylphenidate, possesses pharmacological activity similar to that of other known stimulants (Goodman et al., 2001). It is an oxazolidine compound and is chemically identified as 2-amino-5-phenyl-2-oxazoline-4-one (Markowitz & Patrick, 2001). The chemical structure of Pemoline is illustrated in figure 1.

1.4.2 Preparations of Pemoline:

Pemoline is subject to control under the Federal Control Substance Act of 1970 as a schedule IV (C-IV) drug. Pemoline is supplied as tablets containing 18.75mg, 37.5mg or 75mg of pemoline for oral administration, and it is also available as chewable tablets containing 37.5mg of pemoline (American Society of Hospital Pharmacists, 2002; Express scripts, 2005). Table 1 summarizes pemoline strengths, trade names, product imaging and their manufacturing companies.

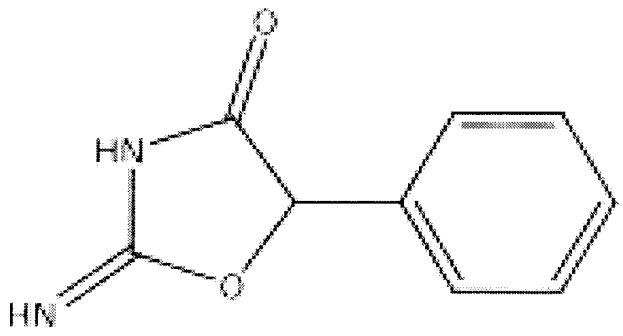
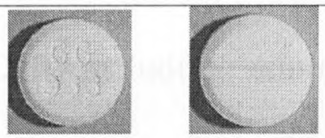
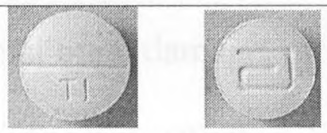
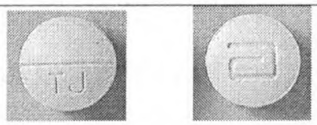
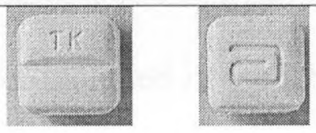


Figure (1): The chemical structure of pemoline.

Dosage form	Strength	Trade names and tablet shape	Manufacturing company
Oral Tablets	18.75 mg*	Cylert® 	Abbott
		Pemoline 	Sandoz
	37.5 mg*	Cylert® 	Abbott
		PemADD® 	Mallinckrodt
	75mg*	Cylert® 	Abbott
		PemADD ®	Mallinckrodt
Tablet chewable	37.5mg*	Cylert® 	Abbott
		PemADD ® Pemoline	Mallinckrodt Teva

* available by nonproprietary name

Table (1): The pemoline strengths, trade names, product imaging and their manufacturing companies.

1.4.3 Indication and Usage of Pemoline:

- Attention Deficit Hyperactivity Disorder:

Pemoline is indicated as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD in children older than 6 years of age. In the past, a variety of terms have been associated with the signs and symptoms of ADHD including: minimal brain dysfunction, hyperkinetic reaction of childhood, hyperkinetic syndrome, hyperactive child syndrome, minimal brain damage, minimal cerebral dysfunction, and minor cerebral dysfunction (Phillip, 2005).

- Other Uses:

Pemoline has been used in the treatment of multiple sclerosis to relieve certain types of fatigue (Bethoux, 2006), narcolepsy (Zeitzer et al., 2006), depression, chronic schizophrenia, and as a mild stimulant for geriatric patients. These uses are not included in the labeling approved by the U.S. Food and Drug Administration (American Society of Hospital Pharmacists, 2002).

1.4.4 Pharmacology of Pemoline:

The pharmacological actions of pemoline are qualitatively similar to those of amphetamine and methylphenidate (Conners & Taylor, 1980; Pelham et al., 1990), and include central nervous system and respiratory stimulation. Unlike most other psychostimulants, pemoline produces no significant peripheral noradrenergic effects (Fuller et al., 1978; Kagan, 1974). The mechanism and site of action of pemoline in humans have not been determined. Limited animal experiments suggest that the central nervous system stimulatory action of pemoline may be mediated by brain dopamine, where pemoline is thought to inhibit the dopamine transporter that blocks the reuptake of dopamine into presynaptic neurons and increases the release of this monoamine into the extraneuronal space (Molina & Orsingher, 1981). This process is shown in figure 2. There is neither specific evidence which clearly establishes the mechanism by which pemoline produces it's mental and behavioral effects in children, nor conclusive evidence regarding how these effects are related to the condition of the central nervous system. Pemoline may produce an increase in motor activity or mental alertness, a diminished sense of fatigue, and mild euphoria. The drug apparently produces an anorexigenic effect. In usual

therapeutic dosage, pemoline exhibits no substantial effects on the peripheral circulatory system (American Society of Hospital Pharmacists, 2002).

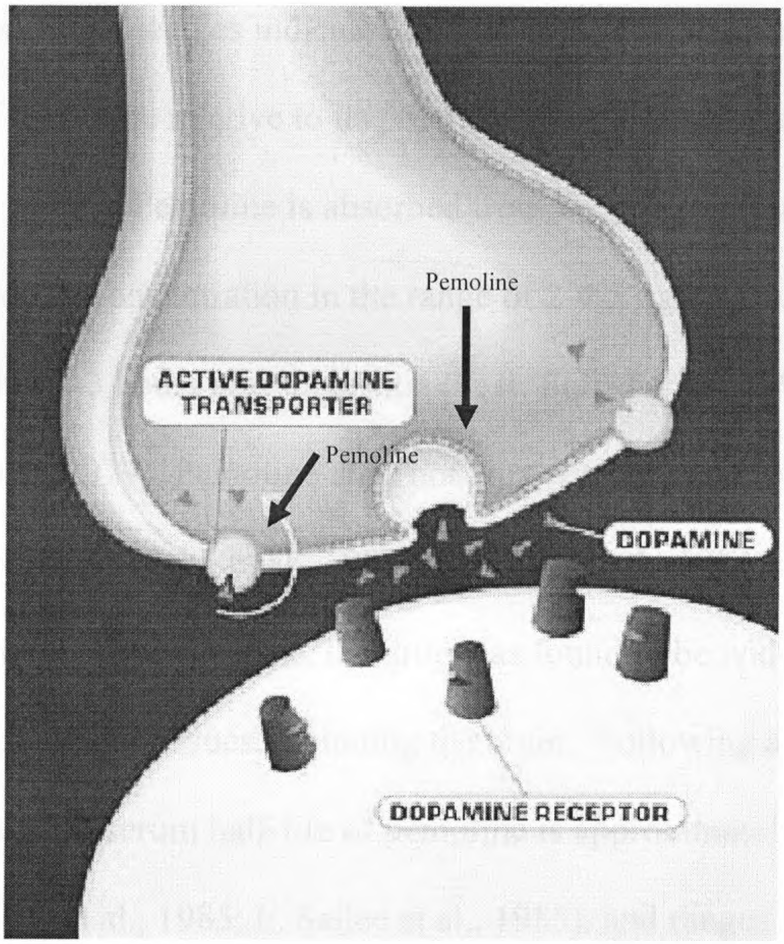


Figure (2): Sites of action of pemoline on the release and reuptake of dopamine at sympathetic neuroeffector junctions

(Annenberg Media, 2006).

1.4.5 Pharmacokinetics of Pemoline:

Pemoline is formulated as a magnesium hydroxide product (formulation of the drug consists of an equimolar ratio of pemoline and magnesium hydroxide) as animal studies indicated that magnesium enhances the absorption of pemoline relative to its practically water-insoluble free form (Lange et al., 1962). Pemoline is absorbed from the gastrointestinal tract, with a peak serum concentration in the range of 2-4.5 μg/ml which is achieved within 2-3 hours after ingestion (F. R. Sallee et al., 1992; Vermeulen et al, 1979). Pemoline does not appear to be significantly bound to plasma proteins (Kotaki, et al., 1988; Nishihara et al., 1984). In animals receiving radiolabelled pemoline, the drug was found to be widely distributed throughout tissues, including the brain. Following a single oral dose, the plasma or serum half-life of pemoline is approximately 7 hours in children (Collier et al., 1985; F. Sallee et al., 1985), and ranges from about 11-12 hours in adults (Collier et al., 1985; Vermeulen et al., 1979). This allows for the single daily dosing of pemoline.

Approximately 90 per cent of pemoline and its metabolites are excreted, primarily in urine. Only negligible amounts are excreted in feces. More than 50 per cent of a single oral dose of pemoline is metabolized, and the other 50 per cent is cleared as a parent compound (Vermeulen et al., 1979).

Pemoline is metabolized to pemoline dione, mandelic acid, and unidentified conjugated and polar products. Large interindividual variability exists in the absorption and disposition of pemoline. At present, it is not known which CYP isozyme(s) mediates the oxidative metabolism of pemoline (F. Sallee et al., 1985).

1.4.6 Dosage and Administration of Pemoline:

Current manufacturer's guidelines for initiating pemoline therapy for the treatment of ADHD disorder in children 6 years of age and older is a single oral dose each morning (to avoid insomnia) of 37.5 mg, with increases of 18.75 mg at one week intervals until the desired clinical response is attained. Most children respond at a dosage range of 56.25-75 mg/day. The maximum recommended daily dose is 112.5 mg. Possibly because of the cautious dosing and titration guidelines offered by the manufacturer (Pelham et al., 1995), therapeutic effects of pemoline may not be achieved until the third or fourth week of therapy (American Society of Hospital Pharmacists, 2002).

1.4.7 Hepatotoxic Risk of Pemoline

Since 1975, when pemoline was approved for use in the United States of America, several cases of acute liver failure, including those resulting in death, have been reported during post marketing surveillance studies of patients receiving pemoline. Pemoline has been associated with liver abnormalities ranging from reversible increases in the liver enzymes that is not associated with symptoms, to irreversible acute liver failure which may result in death (See section 1.5 literature review of pemoline induced hepatotoxicity).

1.4.8 Other Adverse Effects of Pemoline:

Insomnia is the most common adverse effect of pemoline, usually occurring early in the therapy. Pemoline-induced insomnia is usually transient and responds to a reduction in dosage (Pelham et al., 1995; Pelham et al., 1990). Anorexia, stomachache, irritability, and headache may also occur. A temporary reduction in the growth rate of children has also been reported with long term use of pemoline (Friedmann et al., 1981). Compared to other psychostimulants, pemoline appears to have little potential for abuse or dependence (Langer et al., 1986) and, accordingly, has not been subject to

the same scheduling controls as methylphenidate or dextroamphetamine. However, pemoline abuse has been reported (Polchert & Morse, 1985).

1.4.9 Drug Interactions of Pemoline:

There are a few reports of drug-drug interactions with pemoline. An animal study indicated that methylphenidate may increase plasma concentrations of pemoline (Kotaki et al., 1988).

1.5 Literature Review of Pemoline Induced Hepatotoxicity:

Pemoline-induced hepatic injury ranges from asymptomatic increases in serum transaminase levels, which are often reversible upon withdrawal of therapy, to cases of liver failure requiring liver transplantation. As the primary indication for this drug is in the treatment of ADHD in children, most of the adverse cases reported in the scientific literature involve pediatric patients. In the adult population, pemoline-induced hepatotoxicity is reported much less frequently, since the drug is indicated only in specific and relatively rare situations, such as treatment of chronic fatigue in adults with multiple sclerosis (Bakshi, 2003). Most of the cases are characterized by late-onset hepatotoxicity. The mechanisms responsible for pemoline-induced hepatotoxicity are still unknown. There are studies hypothesizing that the mechanism involves an autoimmune reaction (Sterling et al., 1996; Rosh et al, 1998; Hochman et al., 1998); this mechanism is supported by the fact that some cases were positive for different autoantibodies, and that other cases responded to a course of corticosteroid therapy.

In reviewing the literature, 16 reports of 34 cases of pemoline-induced hepatotoxicity have been obtained. These cases range from mild

transient increases of serum transaminase to liver failure, including some deaths. The reports can be categorized into three periods according to their date of reporting. The cases in Section one were reported before the drug was approved to enter into the U.S. market (premarketing); Section two reports cases after pemoline was approved by the FDA (1975) until the year before the introduction of the first warning label (1996) that emphasized the possible association with hepatic failure, and the cases in Section three were reported after the introduction of the warning label.

The details of the cases are as follows:

1- Pre-marketing cases of pemoline induced hepatotoxicity:

In 1973, a study was published about adults older than 60 years of age. The dose of pemoline was between 50-150 (mg/day), for a duration of 1.5 months. Two out of 60 patients developed hepatic abnormalities. These two subjects were later rechallenged with pemoline, and the same liver enzyme elevations occurred (Gilbert et al., 1973). In the same year (1973), there was a report of two adults aged 64 and 80 who developed reversible liver abnormalities (elevated liver enzyme and cellular necrosis) while receiving pemoline for 3 months (Tolman et al., 1973). The third study

(1974), described clinical trials of pemoline in children aged 6 to 12 years, with a daily dose of 75 mg of pemoline per day, for duration of one year. Nine out of 288 children developed elevation in hepatic enzyme levels, two of them were rechallenged with pemoline, and the same hepatic abnormality reoccurred (Safer et al., 2001).

2- Postmarketing cases of pemoline induced hepatotoxicity (1975 to 1995):

These cases that were reported after pemoline was approved by the FDA to enter the U.S. market (1975) and until the year of our index case (1995), which was the year before the introduction of the black box warning of pemoline associated with hepatic failure. The first case was reported in 1984, describing 10-years old boy who received a dose of 75mg/day. After one month of treatment he developed a reversible elevation of liver enzymes (Patterson, 1984). The first two cases of death associated with hepatic failure were reported in 1989. In one of them the death was attributed to toxic hepatitis secondary to pemoline "overdose", and in the second case, the patient had a history of biliary cirrhosis (Jaffe, 1989). In 1990 there were three reports of four cases of children who developed liver toxicity. Two of the children had reversible elevations of liver enzymes (Elitsur, 1990; Pratt & Dubois, 1990) and the third child had liver necrosis (Pratt & Dubois,

1990). The fourth case was severe, the child was subjected to unsuccessful liver transplant and died (Nehra et al., 1990). All four children were treated with pemoline for 5-12 months. In 1995 the index case was reported (Berkovitch et al., 1995) (See Pemoline index case).

3- Cases of pemoline-hepatotoxicity reported after the warning:

There were 12 cases of hepatotoxicity reported between 1996 and 1998. Three of these had a serious outcome which led to liver transplants (Adcock et al., 1998; Rosh et al., 1998). These patients developed liver failure after a long duration of pemoline treatment (7-54 months). The other cases ranged from elevated liver enzymes (3 cases) (Marotta & Roberts, 1998), to jaundice (4 cases) (McCurry & Cronquist, 1997; Rosh et al., 1998; Sterling et al., 1996) and cellular necrosis (2 cases) (Hochman et al., 1998; Marotta & Roberts, 1998). All the above cases were in children except for one adult case that was reported in 1996. The last case reported in the published medical literature was in 2001 (Abbiati et al., 2002). The case was of a 36 year old female, who presented with jaundice, which developed into acute liver failure and required a liver transplant. The patient was prescribed pemoline for off-label purposes for being overweight, taking advantage of

one of pemoline side effects of anorexia, in order to achieve weight loss. The dose of pemoline was 75 mg/day.

In summary the medical literature has reported often an elevated hepatic enzymes, hepatotoxicity and hepatic death associated with pemoline. Despite this trend no previous attempt has been done to prove causality.

CHAPTER TWO: OBJECTIVES AND HYPOTHESIS

Objective:

To create a system that will estimate the potential association between a serious adverse event and a medicinal drug early in its marketing cycle.

Hypothesis:

The new system will illustrate how pemoline-associated acute liver failure (ALF) could have been predicted few years after its marketing by using data existing at that time.

CHAPTER THREE: METHODS

3.1 Research Questions:

The research question of the study was:

1- Is the use of pemoline in children with ADHD associated with an increased risk of acute liver failure?

If question one is answered yes:

2- In what year were there sufficient data to estimate this association, to prevent more children from life threatening exposure?

3.2 Study design:

3.2.1 General Design:

The study was a postmarketing surveillance of pemoline hepatotoxicity based on case reports as show in the diagram in figure 3.

3.2.2 Study Population:

The research started by selecting a defined population, which were children in the U.S. and Canada. Each calendar year after 1975 when pemoline was approved to be marketed as a treatment for ADHD, the number of children who were on pemoline was defined and the number of reported cases of acute liver failure due to pemoline was also determined.

3.2.3 Study Protocol:

After obtaining the data of the number of children on pemoline per year, and the number of children who developed acute liver failure while on pemoline per year, a comparison was made between these data and the background incidence rate of idiopathic acute liver failure in children in the general population. This comparison was made by year, since the drug was approved to be used on the market to define which year the rate of serious

acute liver failure due to pemoline was significantly higher than predicted in the general population.

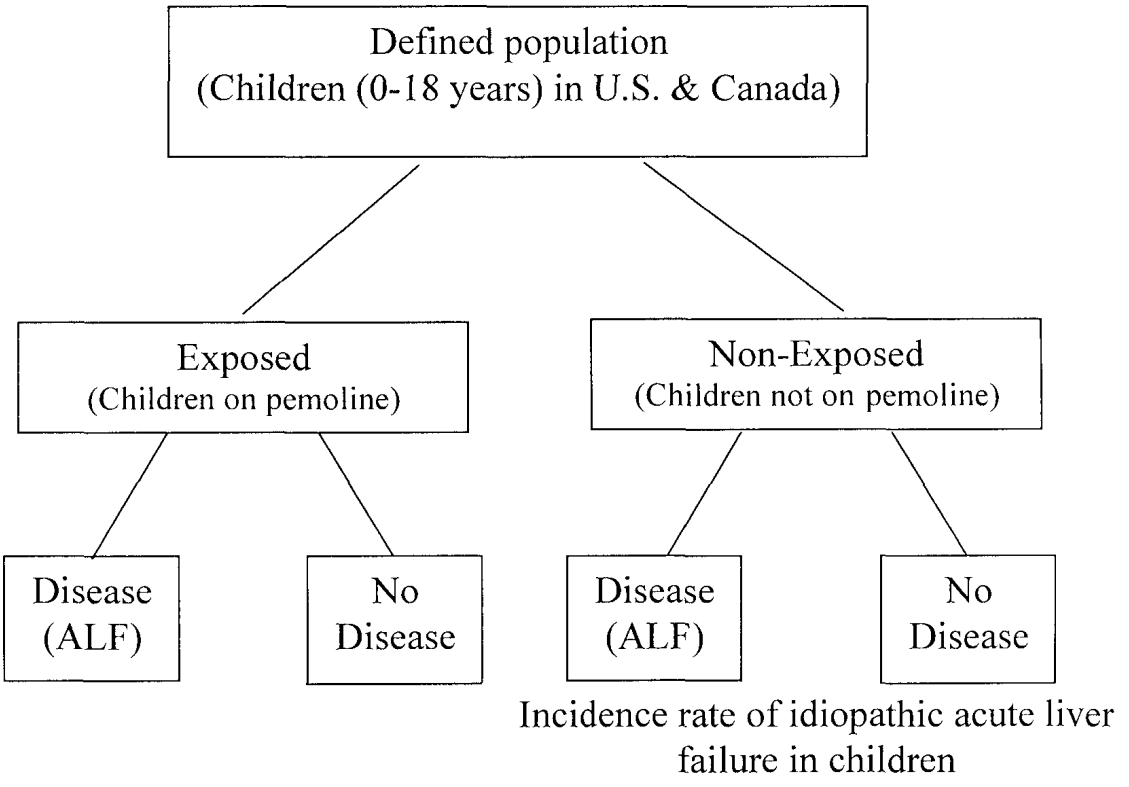


Figure (3): Design of the research study.

3.3 Data Collection:

The collection of data aimed to address the study's research question namely: In what year could the use of pemoline be proven to be significantly associated with increased risk of acute liver failure?

3.3.1 The Rate of Idiopathic Acute Liver Failure in Children:

Data were synthesized from the published literature. We searched PubMed, EMBASE and SCOPUS, using the keywords liver failure, acute, children, fulminate, idiopathic, unknown reason, incidence and epidemiology. Only papers emphasizing the rate of acute liver failure in children and their etiologies, including idiopathic liver failure are included in this analysis.

3.3.2 The Annual Number of Children Treated With Pemoline:

The exposed population for this study was children taking pemoline in Canada and the United States. The information regarding the number of children on pemoline in Canada per year was obtained from IMS (International Medical Statistics) Montreal Quebec. The IMS is a holder of statistical medical information that can be accessed by researchers,

academics and government to advance health. Regarding US data, we gathered the information by synthesizing available published data, by searching in medline and obtaining all articles that mentioned the number of children prescribed pemoline.

3.3.3 The Annual Number of Children on Pemoline in the U.S and Canada Who Developed ALF:

This information was obtained from the FDA under the Freedom of Information Act. All pemoline cases reported to the FDA between 1975 and 1999 where hepatotoxicity was reported were analyzed. The criteria for selection of liver injury cases were: age between 0 and 18 years of age, death due to the use of pemoline therapy and any report of irreversible damage to the liver, where all the cases have to be within the dosages recommended for its primary indication. We excluded cases reporting increased liver enzyme levels that returned to normal once pemoline was discontinued. Only cases of severe irreversible acute liver failure were considered, because in our analysis we used the background incidence rate of idiopathic acute liver failure in children in the general population. Some of these cases have also been published in the literature and these articles were obtained. We used the same criteria for selection of the literature cases as was used in the FDA

cases. All the literature cases were subjected to causality assessment using the Naranjo ADR probability Scale (Naranjo et al., 1981). The Naranjo ADR probability scale is a tool widely used to determine the likelihood that an ADR is caused by the implicated medication. Ten questions are answered and assigned a weighted score of +2 to -2. Where there are insufficient data available, the particular question receives a 0. Based on the Naranjo criteria (Table 2) each case is scored (< 1 - > 9) and assessed a likelihood of causing an ADR from doubtful, possible, probable to highly probable (Table 3).

	Questions	Yes	No	Don't know
1)	Are there previous conclusive reports on this reaction?	+1	0	0
2)	Did the ADR appear after the suspected drug was administered?	+2	-1	0
3)	Did the ADR improve when the drug was discontinued?	+1	0	0
4)	Did the ADR appear with re-challenge?	+2	-1	0
5)	Are there alternative causes for the ADR?	-1	+2	0
6)	Did the reaction appear when placebo was given?	-1	+1	0
7)	Was the drug detected in blood at toxic levels?	+1	0	0
8)	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9)	Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10)	Was the ADR confirmed by any objective evidence?	+1	0	0

Table (2): Naranjo ADRs probability scale criteria

(Naranjo et al., 1981).

Total Score	ADR Probability Classification
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Table (3): Naranjo ADRs probability classification

(Naranjo et al., 1981).

3.4 Data Analysis:

Statistical analysis of the data was done first by calculating the yearly Relative Risk (RR), which is the incidence rate of acute liver failure among individuals exposed to pemoline to the incidence rate of idiopathic ALF in children in the general population. Relative Risk can be calculated using the following simple equation:

Relative Risk (RR) = $[a / (a + b)] / [c / (c + d)]$

a=children on pemoline who develop ALF

b=children on pemoline who didn't develop ALF

c=children not on pemoline who develop idiopathic ALF

d=children not on pemoline who didn't develop ALF

The second statistical analysis was calculating the yearly P-values. P-value was determined by using the chi-square test, unless one cell frequency was less than 5, in which case, the Fisher's exact test was more appropriate since it gives a more conservative P-value. P-values, RR and 95% confidence intervals (CIs) were calculated using the statistical package Epi Info, version 3.3.2-2005 (http://www.cdc.gov/epiinfo/).

The analysis was done twice. The first analysis was done using FDA reports as a source of the data, and the second analysis by using the medical literature cases as a source of data.

CHAPTER FOUR: RESULTS

4.1 The Rate of Idiopathic Acute Liver Failure in Children:

We reviewed the published medical literature on acute liver failure in children. Based on a recent large comprehensive study of fulminant hepatic failure, approximately 230 children are affected each year in the United States (Liu et al., 2001). Since the number of children who live in the United States is 73,043,506 (Children Defense fund, 2000), the overall rate of acute liver failure in children is estimated to be 1:300,000.

All available studies in the published literature reporting on the breakdown of etiologies of ALF in children were reviewed. In total, based on 4 studies 16% of the cases of ALF were due to unknown reasons (idiopathic) (Table 4). From those data, we calculated that the rate of idiopathic liver failure in children is **1:2,000,000**.

Investigator	Years of the study	No. of patients with unknown causes of ALF	Total No. of patients with ALF in the study	Percentage of unknown causes of ALF (%)
(Devictor et al., 1992)	1987-1991	4	35	11.4
(Devictor et al., 1993)	1982-1993	8	56	14.3
(Liu et al., 2001)	1993-2001	11	57	19.3
(Liu et al., 2006)	1993-2003	16	81	19.8
			% of Idiopathic Acute liver Failure	16%

Table (4): Medical literature reports of percentage of idiopathic ALF in children.

4.2 The Yearly Number of Children Taking Pemoline in the U.S.:

Data were extracted from the published medical literature. We identified five papers that surveyed the prevalence of medication use to treat children with ADHD in the U.S. The yearly percentage of American school children on ADHD medication from 1975 through 1993 was calculated (Table 5) and for any missing year for which no publication existed we estimated the mean value from the closest years before and after. The percentage of children receiving treatment with stimulant medication for ADHD ranged between 2.1% to 6%. In addition, we identified the percentage of pemoline use among ADHD children, which was 1% in 1975 and increased gradually to 6% in 1987. Between 1987 and 1993, there was no data available on the percentage of pemoline use among ADHD children, so we assumed that the percentage was not changed since 1987. The yearly number of school children in the U.S. has been obtained from international historical statistics (The Americas) (Mitchell, 2003). Based on the above information, we calculated the number of children taking pemoline annually in the U.S. Table (6) summarizes these findings.

Year of the study	Investigator	% of children on ADHD medication	% of ADHD children medicated on pemoline
1975	(Krager et al., 1979)	2.08	1
1977	(Krager et al., 1979)	2.12	5.7
1979	(Safer & Krager, 1983)	2.43	—
1981	(Safer & Krager, 1983)	2.65	—
1983	(Safer & Krager, 1985)	3.61	—
1987	(Safer & Krager, 1988)	5.96	6
1993	(Safer & Krager, 1994)	3.58	—

Table (5): Literature reports of U.S. school children on ADHD medication and on pemoline therapy from 1975 to 1993.

Years	No. of U.S. school children in U.S.	Percent on ADHD medication %	No. of children on ADHD medication	Percent on pemoline %	No. of children on pemoline in the U.S.	Cumulative No. of children on pemoline in the U.S.
1975	49,791,000	2.08	1,035,653	1	10,357	10,357
1976	49,484,000	2.1	1,039,164	3.35	34,812	45,169
1977	48,711,000	2.12	1,032,673	5.7	58,862	104,031
1978	47,636,000	2.275	1,083,719	5.73	62,097	166,128
1979	46,645,000	2.43	1,133,474	5.76	65,288	231,417
1980	46,318,000	2.54	1,176,477	5.79	68,118	299,535
1981	45,599,000	2.65	1,208,374	5.82	70,327	369,862
1982	45,252,000	3.13	1,416,388	5.85	82,859	452,721
1983	45,067,000	3.61	1,626,919	5.88	95,663	548,383
1984	44,993,000	4.1975	1,888,581	5.91	111,615	659,999
1985	45,066,000	4.785	2,156,408	5.94	128,091	788,089
1986	45,289,000	5.3725	2,433,152	5.97	145,259	933,348
1987	45,371,000	5.96	2,704,112	6	162,247	1,095,595
1988	45,438,000	5.5633	2,527,852	6	151,671	1,247,266
1989	45,821,000	5.1666	2,367,388	6	142,043	1,389,309
1990	46,424,000	4.7699	2,214,378	6	132,863	1,522,172
1991	47,264,000	4.3733	2,066,997	6	124,020	1,646,192
1992	48,196,000	3.9766	1,916,562	6	114,994	1,761,186
1993	49,416,000	3.58	1,769,093	6	106,146	1,867,331

Table (6): The calculated number

of children on pemoline in the U.S. per year.

4.3 The Number of Children Taking Pemoline Per Year in Canada:

The I.M.S. Inc. (Montreal, Quebec) provided us with the yearly number of pemoline prescriptions dispensed by Canadian retail pharmacies from 1987 until 2004. Due to privacy issues, which restrict the company from measuring how many individual patients took the drug, only the number of prescriptions was available. I.M.S. calculated that the average prescription of pemoline in Canada contained 62.5 units (tablets), and we assumed that, a typical child received one tablet per day for one year. Hence:

The Number of Children on Pemoline each year =
Number of Pemoline Prescriptions Dispensed from Canadian Retail pharmacies X 62.5 / Number of days in the year (365).

Although, the overlap of users from year to year could not be found we assumed that this overlap is not significant.

Based on the above metrics we calculated that a total of 45,404 Canadian children were treated with pemoline from 1978 to 2004 (Table 7).

Figure (4) represents the cumulative chart of children taking pemoline from 1987 to 2004 in Canada, where in 2000 the drug was taken off the market. The FDA approved the marketing of pemoline in 1975, while in Canada the marketing of the drug started only in the eighties. The Canadian Drug Identification Codes are drug product database books published annually. I found that the first time pemoline was included in these databases was in 1981 (Canada Drugs Directorate, 1981). Also, the first time pemoline was included in The Compendium of Pharmaceuticals and Specialties (Canadian Pharmaceutical Association, 1986) was in 1986.

Years	No of pemoline Rx	No of children on pemoline	Cumulative No of children on pemoline
1987	3,000	514	514
1988	6,000	1027	1,541
1989	8,000	1370	2,911
1990	10,000	1712	4,624
1991	11,000	1884	6,507
1992	18,000	3082	9,589
1993	24,000	4110	13,699
1994	28,000	4795	18,493
1995	34,000	5822	24,315
1996	43,000	7363	31,678
1997	35,000	5993	37,672
1998	29,000	4966	42,637
1999	16,000	2740	45,377
2000	52	9	45,386
2001	42	7	45,393
2002	-	0	45,393
2003	3	1	45,394
2004	59	10	45,404

Table (7): The calculated number of children on pemoline for each year in Canada from 1987 to 2004.

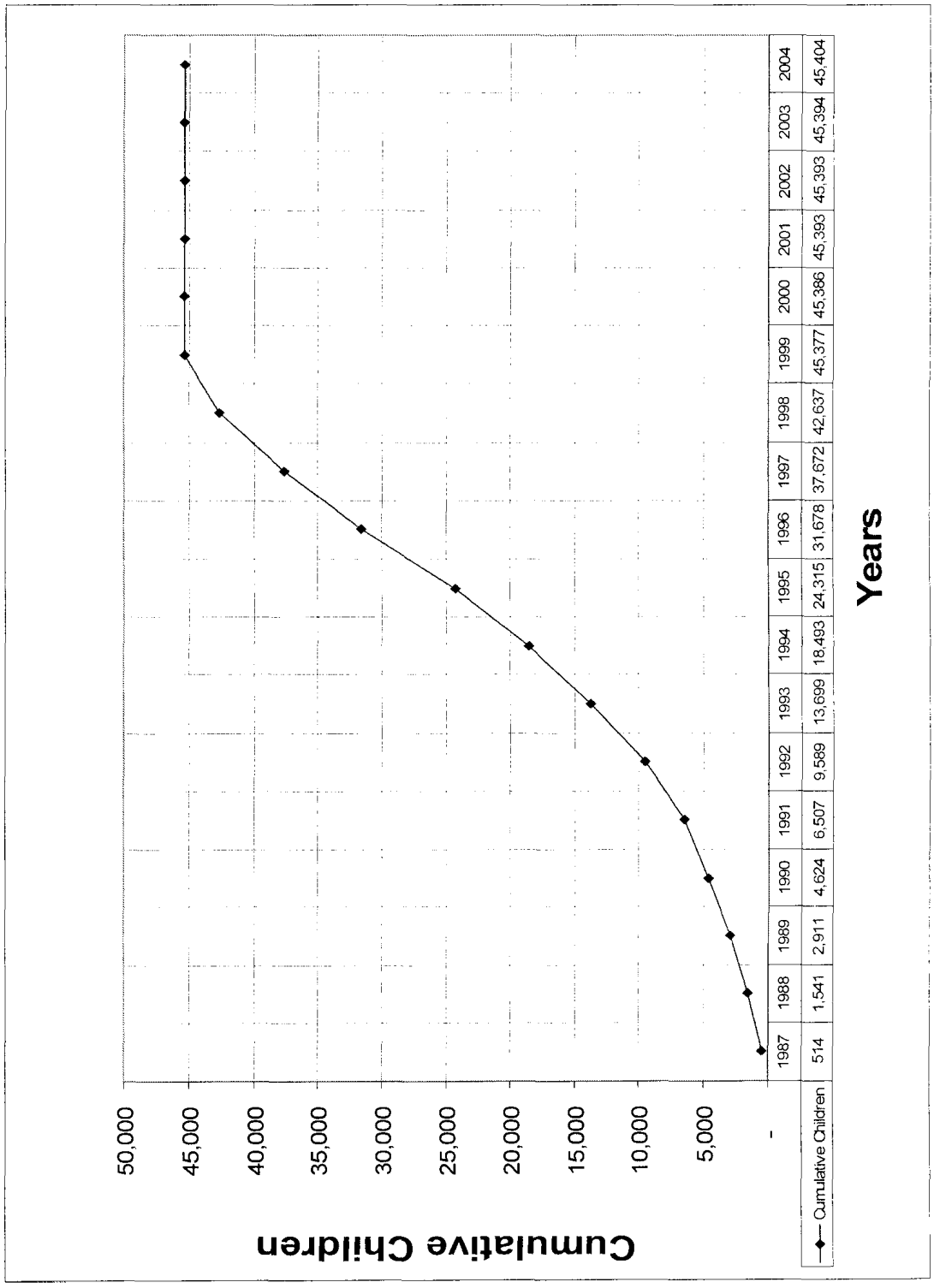


Figure (4): Cumulative chart of children taking

Pemoline for an entire year from 1987 to 2004 in Canada.

4.4 The Number of Children on Pemoline in the U.S. and Canada Who Developed ALF per year:

4.4.1 ALF Cases in Children Receiving Pemoline and Reported to the FDA:

Two hundreds and fifty two cases of elevated hepatic enzymes and hepatotoxicity reported to the FDA from 1975 to 1999 where the patients were under pemoline therapy were obtained under the Freedom of Information Act. Only thirty cases of children met the inclusion criteria who developed serious ALF to be included in the study analysis. The first case was in 1977. Table (8) shows the clinical details and the outcome of these thirty cases. Figure (5) shows for each calendar year the number of FDA cases who developed ALF while on pemoline and the number of children receiving treatment with pemoline in U.S. Canada..

4.4.2 Peer Review Reports of Hepatotoxicity and Death Ascribed to Pemoline:

All articles on pemoline hepatotoxicity that appeared in Medline, and that met the selection criteria for cases were reviewed. Table (9) presents the clinical cases reported in the medical literature for hepatotoxicity and

hepatic deaths in children receiving pemoline. The first case of a hepatotoxicity death due to pemoline occurred in 1977, and was reported in 1989. The total number of cases was 11, and most of them were reported in 1998. Figure (6) presents the yearly cumulative number of FDA ALF cases while on pemoline as well as the cases found in the medical literature.

All literature cases were subjected to causality assessment by using the Naranjo ADR probability scale. Table (10) shows the causality score of these cases. The Naranjo ADR probability scale yielded one case that was classified as "possible" and 10 cases as "probable."

Case No.hi	Year	Age (yr)	Clinical Presentation	Outcome
1	1977	-	Liver damage	Death
2	1978	10	Liver damage	Death
3	1981	12	Toxic hepatitis	Death
4	1984	7	Necrosis/Fibrosis	-
5	1986	11	Hepatic failure	Liver Transplant
6	1988	child	Hepatic Encephalopathy	Death
7	1989	11	Cryptogenic Cirrhosis	Liver Transplant
8	1990	11	Hepatic Necrosis / coma	-
9	1990	8.5	Hepatic Cirrhosis	Liver Transplant
10	1992	-	Fatty Liver	-
11	1992	12	Hepatocellular Necrosis and Gastrointestinal bleeding	Death
12	1993	7	Liver Fibrosis	-
13	1993	18	Liver Failure	Liver Transplant
14	1993	14	Liver Failure	Liver Transplant and Death
15	1993	7	Liver Failure	Death
16	1993	15	Chemical Hepatitis	-
17	1994	18	Liver Damage	Liver Transplant
18	1994	15	Drug Induced Hepatitis	-
19	1994	5	Hepatitis	-
20	1995	7	Liver failure	Death
21	1995	9	Stevens-Johnson Syndrome	Unknown
22	1995	13	Hepatic Failure and Hepatic encephalopathy	Liver Transplant and Death
23	1996	14	Liver Failure	Liver Transplant
24	1996	-	Liver Failure	Liver Transplant
25	1996	7	Liver Damage and Portal Hypertension	Unknown
26	1996	10	Serious Hepatic Problem	Unknown
27	1996	8	Enlarged Liver	Unknown
28	1996	9	Hepatitis	Unknown
29	1997	17	Hepatomegaly and Hepatitis	Continues
30	1998	7	Acute Hepatic Failure with features of Autoimmune Hepatitis and Liver necrosis	-

Table (8): Clinical details of 30 cases with pemoline-induced hepatotoxicity reported to the FDA from 1975 to 1998.

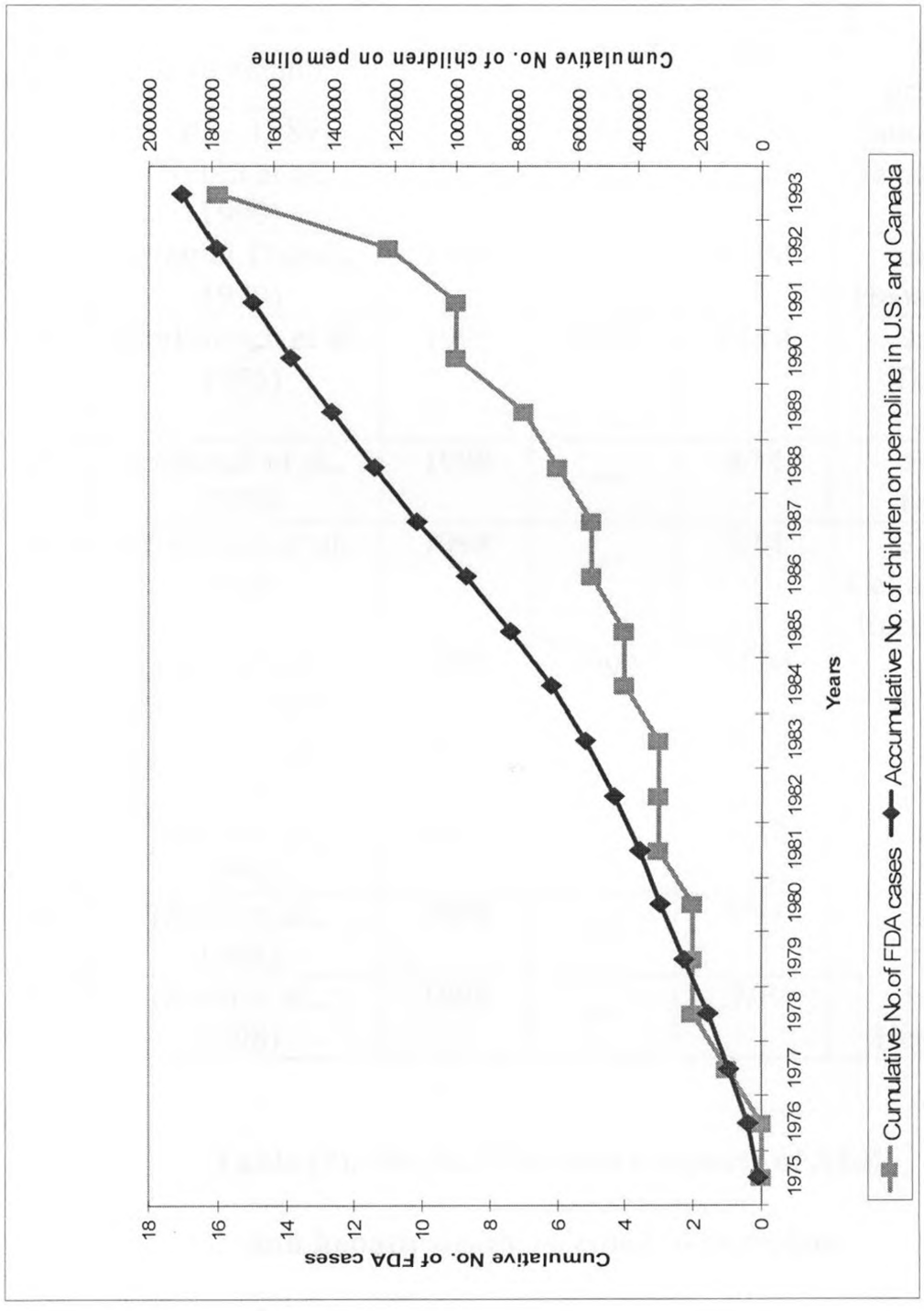


Figure (5): Cumulative chart of children developing ALF after taking pemoline and children on pemoline, from 1975 to 1993 in U.S. and Canada.

Case No	Investigator	Report year	Year of event	Age (yr)/sex	Clinical presentation
1	(Jaffe, 1989)	1989	1977	10/M	Jaundice, Death
2	(Nehra et al., 1990)	1990	1980	12/M	Jaundice, Death
3	(Pratt & Dubois, 1990)	1990	—	11/M	Jaundice, Hepatic necrosis
4	(Berkovitch et al., 1995)	1995	1993	14/M	Jaundice, Transplant, Death
5	(Adcock et al., 1998)	1998	—	9/M	Jaundice, Transplant
6	(Hochman et al., 1998)	1998	—	7/M	Jaundice, Cellular necrosis, Encephalopathy
7	(Marotta & Roberts, 1998)	1998	1992	14/M	Jaundice, Cellular necrosis
8	(Rosh et al., 1998)	1998	—	14/F	Jaundice, Transplant
9	(Rosh et al., 1998)	1998	—	6/M	Jaundice, Transplant
10	(Rosh et al., 1998)	1998	—	7/M	Jaundice, necrosis
11	(Rosh et al., 1998)	1998	—	7/F	Jaundice, Hepatmegaly

Table (9): Medical literature reports of ALF and hepatic death ascribed to pemoline.

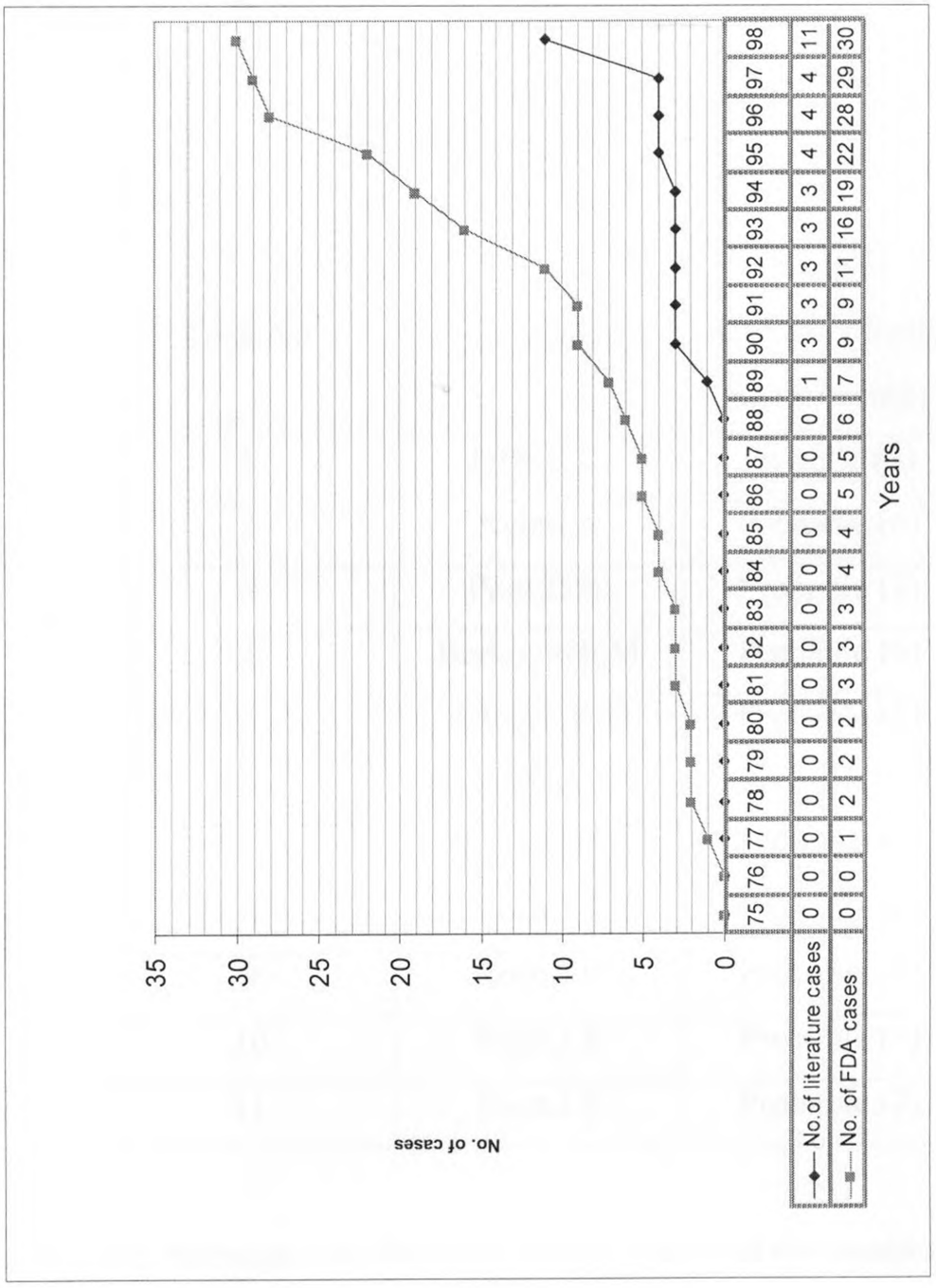


Figure (6): Cumulative chart of children developing ALF after taking pemoline from 1975 to 1998 (the cases from the FDA and the medical literature).

Case No	Investigator	Naranjo Causality Scale (actual score)
1	Jaffe,S.L.	Possible (3)
2	Nehra,A	Probable (6)
3	Pratt,D.S.	Probable (7)
4	Berkovitch,M	Probable (6)
5	Adcock,K.G	Probable (6)
6	Hochman,J.A	Probable (7)
7	Marotta,P.J.	Probable (7)
8	Rosh,J.R	Probable (6)
9	Rosh,J.R	Probable (6)
10	Rosh,J.R	Probable (5)
11	Rosh,J.R	Probable (7)

Table (10): Naranjo causality assessment scores of the medical literature reports of ALF ascribed to pemoline.

4.5 The Data Analysis of Children on Pemoline Developing ALF From 1977 to 1993:

4.5.1 By Using the FDA Reports as a Source of the Data Analysis:

Each year the relative risk of children on pemoline developing ALF was high, between 9.12 and 24.08. The highest RR was detected in 1978, as shown in figure (7) and table (11), which also shows the 95% confidence interval of the RR. All these values were significant, with the 95% C.Is. being above 1.

The P-values were calculated for each year using the Fisher exact test. To detect the first year where pemoline could have been associated with ALF, the P-value had to be equal to or less than the widely accepted significance level of 0.05. We found that as early as 1978 the P-value of the association between pemoline and ALF was 0.0053 (figure 8) (table 12). Hence, as early as 1978, a significant signal existed indicating that pemoline is associated with ALF, this is 16 years before the first literature suggestion by Berkovitch and colleagues, 22 years before removal of the medication from the Canadian market and 28 years before removal from U.S. market.

4.5.2 By Using the Medical Literature Cases as a Source of Data:

We repeated the calculation of the yearly relative risk and statistical likelihood of children on pemoline developing ALF from 1977 to 1993 using the ***published cases*** as the source of the cumulative information. We have chosen the first four published cases because we had the data on the yearly number of children under pemoline treatment (See Table 13). The first case (Jaffe, 1989) was reported in 1989, but the hepatic death happened in 1977. The analysis started at the date of the event, and this first case did not show an apparent association. The second case (Nehra et al., 1990) was reported in 1990, but the death had occurred in 1980. Inclusion of this case shows a significant association with pemoline (RR=13.35, 95% confidence interval, 2.59 to 68.83, $P<0.05$). The third case (Pratt & Dubois, 1990), reported in 1990, and did not mention the date of the event, so we assumed that the date of the report was the same as the date of the incidence. With this case, the significant association achieved with the second case, was "diluted", because of the 10 years without any report of ALF. The fourth case (Berkovitch et al., 1995) which was reported in 1995 and the ALF occurred in 1993, returned the association to significance (RR=4.25, 95% confidence interval, 1.14 to 15.84, $P<0.05$).

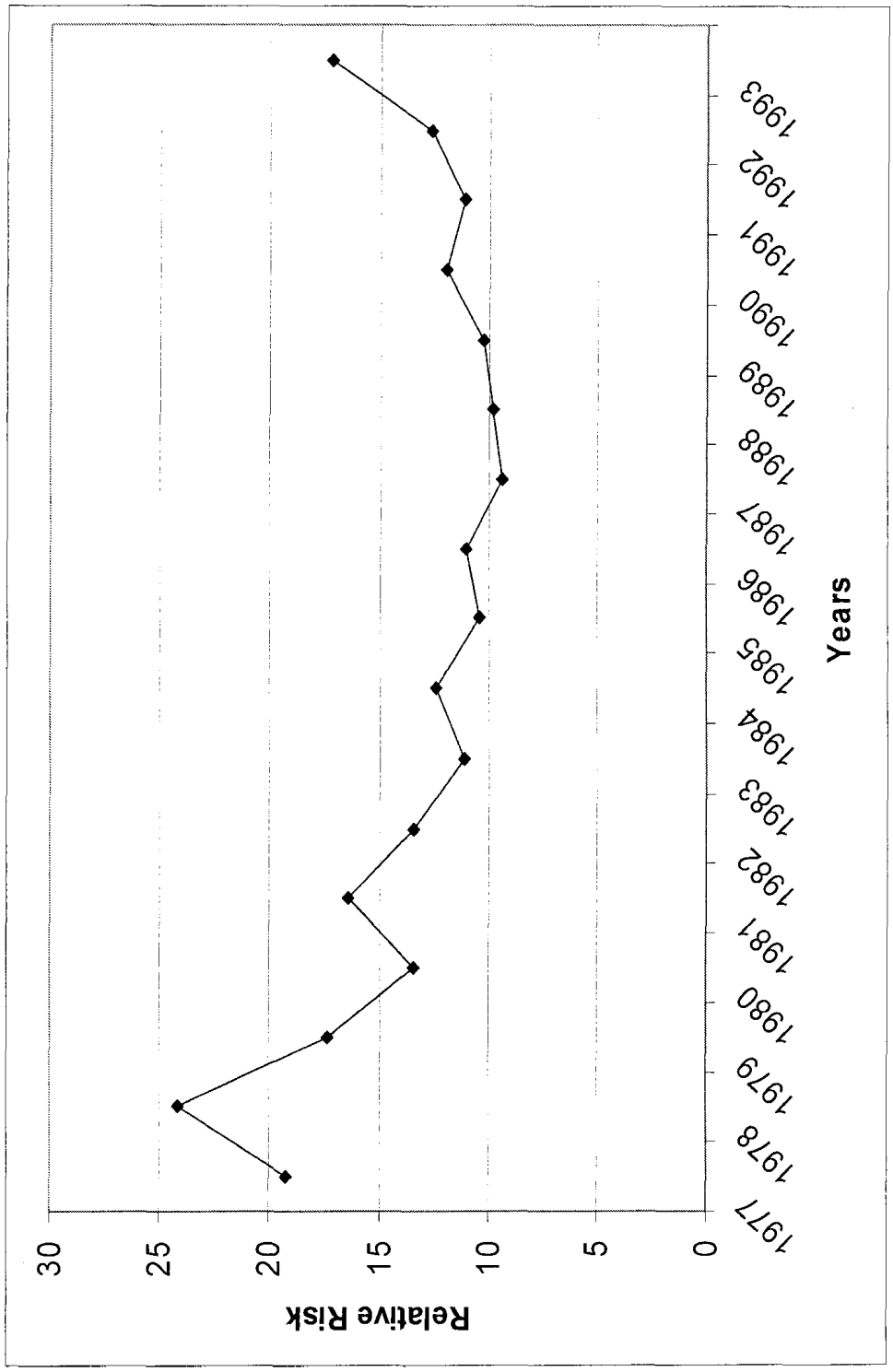


Figure (7): Relative Risks of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports).

Years	RR	95% Confidence intervals
1977	19.22	2.25-164.56
1978	24.08	4.67-124.10
1979	17.28	3.35-89.09
1980	13.35	2.59-68.83
1981	16.22	3.88-67.88
1982	13.25	3.17-55.46
1983	10.94	2.61-45.78
1984	12.12	3.25-45.14
1985	10.15	2.73-37.80
1986	10.71	3.10-37.01
1987	9.12	2.64-31.51
1988	9.61	2.93-31.49
1989	10.06	3.19-31.68
1990	11.79	3.95-35.18
1991	10.89	3.65-32.50
1992	12.42	4.32-35.76
1993	17.01	6.23-46.44

Table (11): The yearly Relative Risk and 95% confidence intervals of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports).

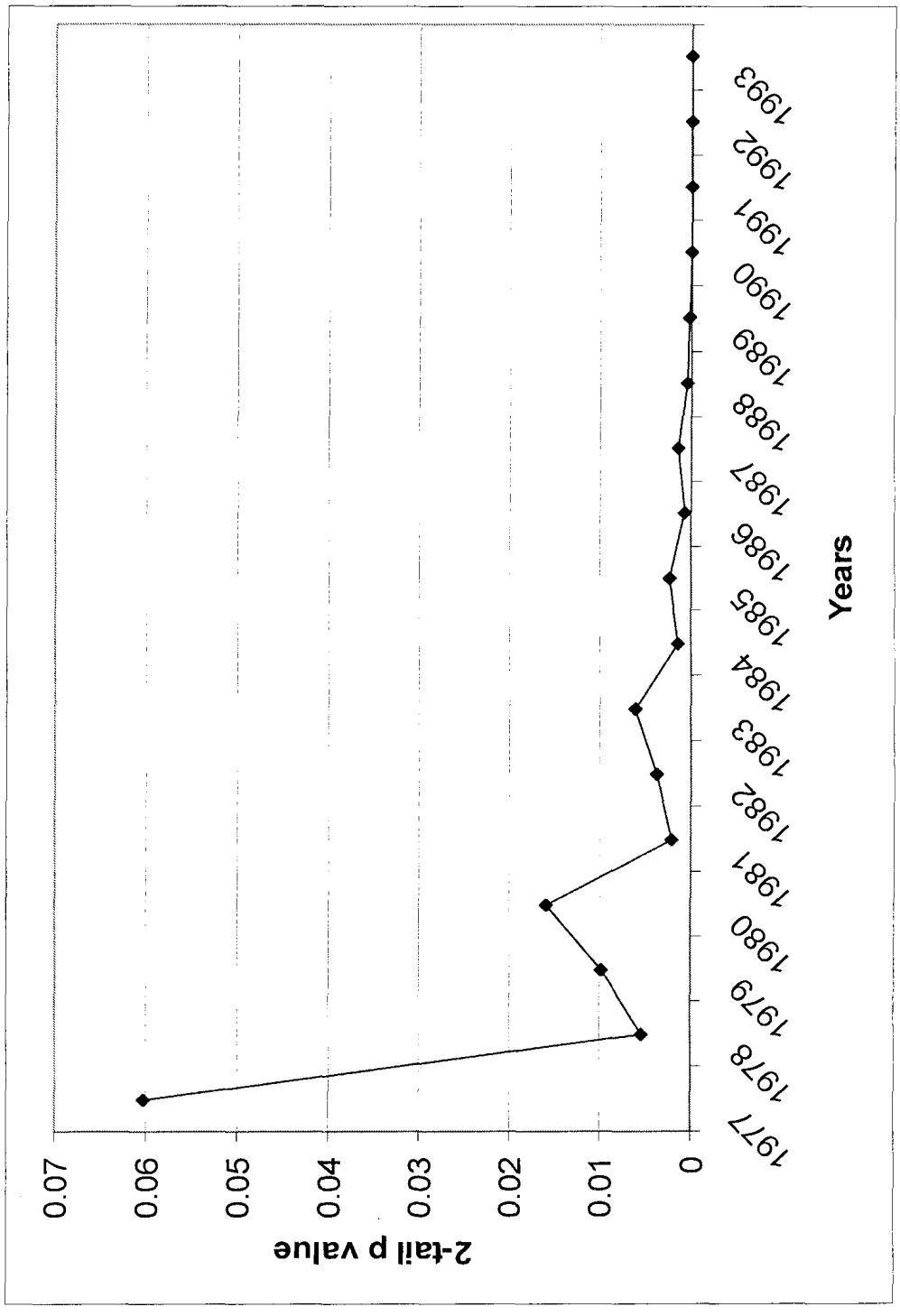


Figure (8): P-values from the Fisher exact test of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports).

Years	P-values
1977	0.0602
1978	0.0053
1979	0.0099
1980	0.0161
1981	0.0022
1982	0.0038
1983	0.0064
1984	0.0014
1985	0.0026
1986	0.0007
1987	0.0015
1988	0.0005
1989	0.00018
1990	0.0000133
1991	0.0000235
1992	0.0000019
1993	1.85E-07

Table (12): P-values from the Fisher exact test of children on pemoline developing ALF from 1977 to 1993 (cases from the FDA reports).

Years	Cumulative No of literature reports	P-values	RR	95% confidence interval
1975	0	0	-	-
1976	0	0	-	-
1977	1	0.06	19.22	2.25-164.56
1978	1	0.0941	12.04	1.41-103.05
1979	1	0.1282	8.64	1.01-73.98
1980	2	0.0161	13.35	2.59-68.83
1981	2	0.0237	10.81	2.10-55.74
1982	2	0.034	8.84	1.71-45.54
1983	2	0.0476	7.29	1.42-37.60
1984	2	0.0653	6.06	1.18-31.24
1985	2	0.0875	5.08	0.98-26.16
1986	2	0.1146	4.29	0.83-22.09
1987	2	0.1466	3.65	0.71-18.81
1988	2	0.1776	3.2	0.62-16.51
1989	2	0.2071	2.87	0.56-14.81
1990	3	0.0777	3.93	0.94-16.44
1991	3	0.0919	3.63	0.87-15.19
1992	3	0.1059	3.39	0.81-14.18
1993	4	0.0405	4.25	1.14-15.84

Table (13): Relative Risks and P-values of children on pemoline developing ALF from 1977 to 1993 (cases from the medical literature).

CHAPTER FIVE: DISCUSSION

5.1 Discussion of Findings:

The underlying goal of my thesis was to develop a novel system of early detection of serious ADRs for newly marketed medications. Using the pemoline example, we were able to show that by knowing how many people are using the drug, one can estimate the incidence rate of serious ADRs early in the marketing cycle, and by comparing it with the incidence rate of the same idiopathic organ failure in the general population.

The major findings of this research are as follows:

1- The incidence rate of acute liver failure in children was estimated to be 1:300,000. About 16 per cent of these cases are idiopathic with a resulting annual incidence of one case per two million children in the general population. In other words, 1:2,000,000 is the background incidence rate of idiopathic acute liver failure in children in the general population, which is considered a rare disorder in children. This baseline frequency of serious adverse events should be considered in postmarketing surveillance studies of the medication. Thus, when a child taking a specific medication suddenly develops unexplained acute liver failure, and all other known

causes have been ruled out, the cause for this adverse event may be the drug itself or yet another unknown cause; which means that the acute liver failure is idiopathic. The use of our proposed novel surveillance method, which has been described in this project, can be very useful in showing or refuting an association between a drug and the specific adverse event. The more cases of an adverse event that are reported and the lower the background incidence of the idiopathic adverse event, the more likely that an association between the drug and the adverse event can be demonstrated or refuted.

2- Our study documents that the prevalence of pemoline use for the treatment of ADHD in children in the U.S. increased approximately ten-fold from 0.02 % in 1975 to 0.22 % in 1993. This is due to two factors. First, more children were treated with ADHD medication, and second, the use of pemoline treatment for ADHD increased from 1 % to 6 % of all medications taken for ADHD since its introduction in 1975 to 1987 (See table 6). This agrees with a previous conducted study in the U.S. (Safer et al., 2001) which showed that the range of pemoline treatment prevalence increased three-fold from 0.08%-0.19% in 1987 to 0.22%-0.64% in 1996. The treatment prevalence of pemoline among U.S. school children kept increasing despite the reports of hepatic toxicity in which pemoline was the primary suspected

factor. This was due to the delay in awareness of the association between pemoline and ALF that should have been highlighted in a black box warning label. The black box warning label first appeared only in 1996 indicating risk of acute liver failure with pemoline use. The label warned that the drug should be used as a second line therapy for the treatment of ADHD. The warning came out almost 19 years after the first case of ALF associated with the pemoline therapy was reported. In 1999 the label was further modified to state that drug users must have their liver enzyme levels monitored at baseline and at biweekly intervals. After these modifications on the labels, a retrospective cohort study conducted in the U.S. between 1998 and 2000 to assess the compliance with the above recommendations was reported (Willy et al., 2002). The results revealed low compliance with both recommendations in the U.S.

In Canada (table 7), the drug was introduced in the 1980s and over the years became more popular until the introduction of the first warning label in 1996. This happened soon after Dr. Berkovich and colleagues published the index case (Berkovitch et al., 1995), creating awareness of the potential serious liver effects of pemoline. The publication appears to have been effective, as most Canadians immediately complied with the warning label by reducing the drug's use. This is shown by a sudden decline in the number

of prescriptions of pemoline issued in 1997 by Canadian physicians (figure 9). In subsequent years the number of prescriptions kept declining until Health Canada decided to take the drug off the market in 2000 (Hogan, 2000).

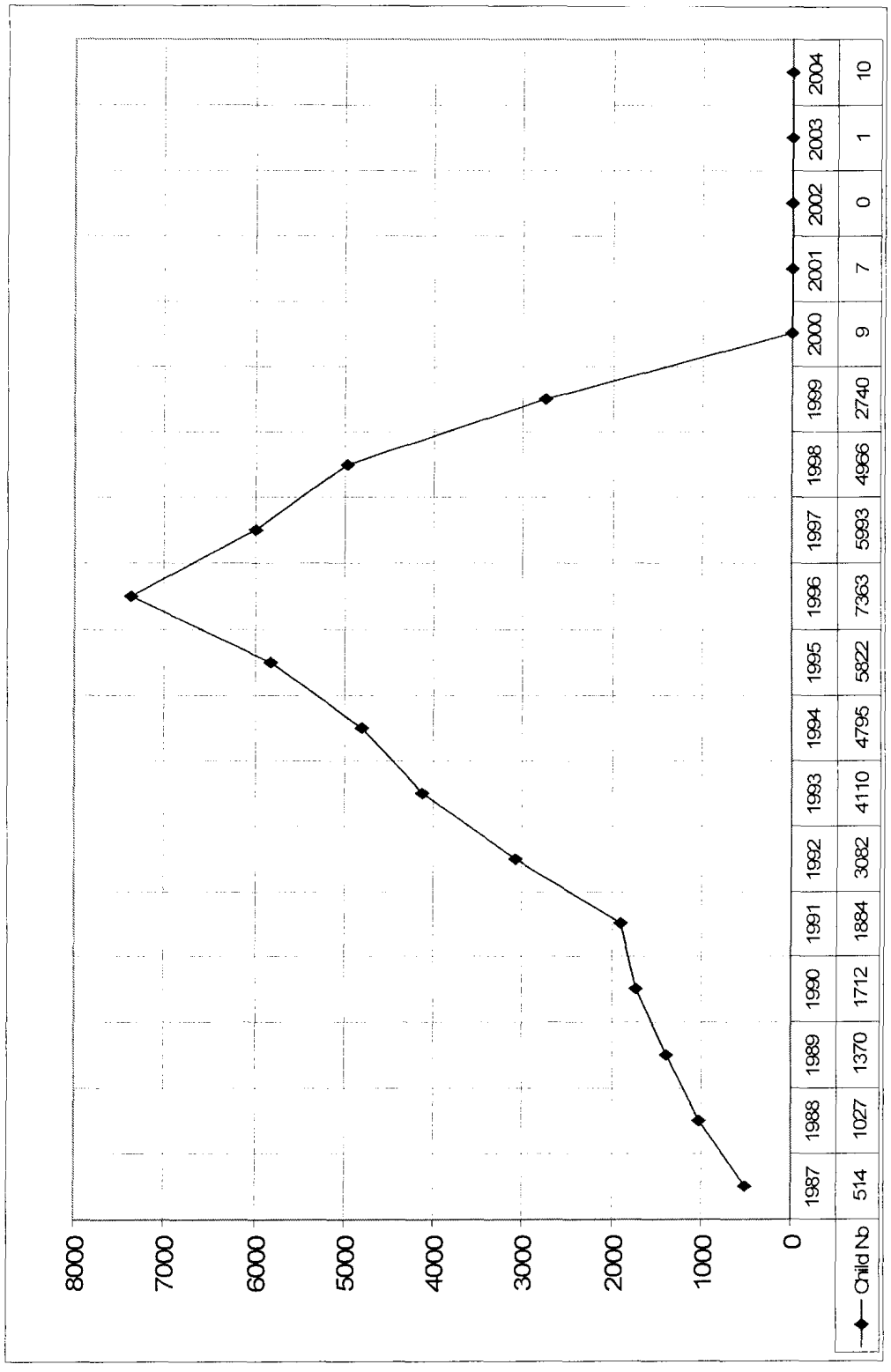


Figure (9): Number of children taking pemoline from 1987 to 2004 in Canada.

3- The first hepatotoxic death reported to the FDA, where pemoline was suspected to have caused the liver damage, occurred in 1977. The event was only two years after the drug was first introduced into the U.S. market. Between 1975 and 1998, among the numerous cases reported to the FDA, we have chosen 30 serious cases for my analysis, all involving children between the ages of 0 and 18 years. This included nine cases of hepatic death and seven cases of liver transplant. The rest of the cases also had serious adverse outcomes. All the chosen cases met the selection criteria listed in the methods section.

In general, I have found that the FDA reports were very hard to use as a set of complete data. There was considerable missing information, especially with respect to the follow up data, and there was also repetition of the same cases. In 1998, the FDA created the office of post-marketing Drug Risk Assessment, and expanded its operation by hiring more staff to deal with reported ADRs. Despite these efforts, the information has not been easily accessible by interested parties, such as academics and medical practitioners (Moore et al., 1998).

4- A smaller number of serious pemoline hepatotoxicity reports were published in the medical literature, compared to the actual number of cases

reported to the FDA. The ratio was about 1:3. The first reported case of death occurred in 1977, but it was not published until 1989. Over the span of eleven years, from 1977 to 1989, only cases with mild hepatotoxicity were published, such as elevated liver enzymes in which the drug user completely recovered after the pemoline treatment was discontinued. Before pemoline was even introduced into the market, there were cases of elevated liver enzymes observed in the clinical trials (See Literature Review of Pemoline Induced Hepatotoxicity). The clinical trials cases should have been taken more seriously as they were potential indicators of problems that arose after the drug became more common prescribed. The 11 selected published cases were subjected to causality assessment using Naranjo ADR probability scale, where 10 out of 11 cases were assigned a likelihood score of 'probable' and one case was classified as 'possible.' The interpretation of these results is that this clinical event, with a reasonable temporal relationship to the administration of the drug, is unlikely to be attributed to the concurrent disease or other drugs or chemicals. (Edwards & Aronson, 2000). Moreover, none of the cases were considered 'highly probable.' Because of the retrospective nature of the study, the application of the Naranjo scale was limited as many of the questions regarding previous exposure, re-challenge and placebo response remained unanswered, and

therefore received a score of 0.There was only one case with the likelihood scale of 'possible', which was a case where the patient had a history of biliary cirrhosis at age six (Jaffe, 1989). Hence, there was an alternative cause for the ADR.

5-Data analysis was performed for each calendar year from 1977 to 1993, where the source of the data was from the FDA reports. In order to determine the year in which the association of pemoline with ALF became significant, the RR and p-values were calculated for each year, which showed that 1978 was the first year to yield an estimated 24 fold increased risk of ALF due to the use of pemoline compared to the incidence rate of idiopathic ALF in the general population (RR 24.08, 95% confidence interval 4.67-124.1) ($p<0.05$). In the following years, the level of significance kept increasing as more cases appeared (See figure 8).

If the information about the unfavorable ALF effects of pemoline had been available and if a similar analysis had been done earlier, as soon as the first cases were reported, many children would not have been put at risk and some children would not have died. The warning label could have been introduced earlier and the withdrawal of the drug could have been

implemented without delay especially as there were other effective alternative treatments for ADHD available.

The data analysis using the medical literature as the source of the ALF cases shows poor and unpredictable reporting of serious ADRs in the literature. There was an apparent significant association in 1980 which could have only been known in 1990 when the case was first published. The significant association of pemoline use with ALF could only have been detected from the medical literature 22 years after the association could have been established using the FDA database (See Figure 10).

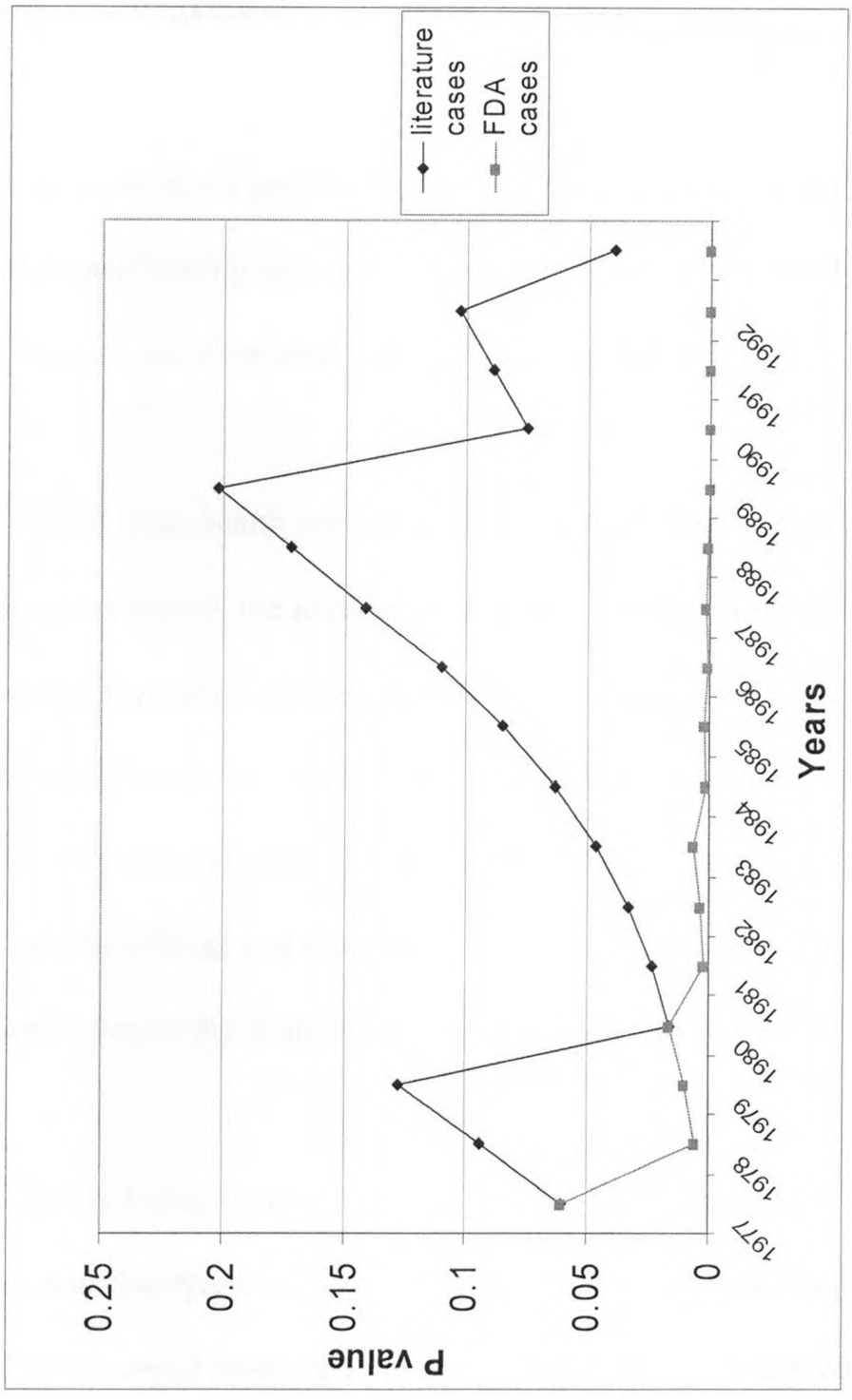


Figure (10): P-values from the Fisher exact test of children on pemoline developing acute liver failure from 1977 to 1993 (cases from the FDA reports and from literature reports)

5.2 Study Limitations:

There is always a probability for false positive or false negative results when performing data analysis. In the context of this study, the possible reasons for these errors are discussed as follows:

1- There is no health service system that contains the data on medication prevalence, the number of drug users in specific jurisdictions, and detailed information on each patient's characteristics. This may be a potential limitation to the study if there was an over estimation of the number of drug users (increase in the cell **b** in the 2x2 table). As a result the signal would be diluted and there would be a delay in recognition of the association between the drug and the adverse event and vice versa.

2- The voluntary reporting system of the FDA appeared to be inefficient and disorganized. There was incomplete information provided to the FDA which could have led to under reporting of adverse events. The underreporting (decrease in the cell **a** in the 2x2 table) would also lead to false negative results (dilution) where the signal of the association is not be established in its appropriate time.

3- The incidence rate of idiopathic liver failure in children was based on systemic review of all studies covering the years from 1982 to 2003. Yet these numbers are relatively small. If the calculated incidence was falsely high, this would give a high background incidence of idiopathic liver failure in the general population (decrease in the cell **d** in the 2x2 table) and the potential signal would be diluted. The opposite would be happen if the calculated incidence was falsely low.

However, our new system was not intended to create an accurate RR rather it aimed at creating a signal that should lead to in depth investigation. In this context it is very unlikely that RR of 5,10 or 15 would be artificially produced by minor inaccuracies.

5.3 Implications of the Study for Clinical Practice:

1- After the introduction of a new drug on the market, the medication use prevalence based on sales should have been known to the manufacturer and should be made available to determine the number of drug users.

2- If there are serious adverse events suspected with the use of drug, especially ones that may cause death or organ failure, they should be assessed completely and reported immediately with effective follow up procedures.

3- Knowing the number of users of a particular medication, along with the number of cases of the specific adverse event, can enable the appropriate drug regulatory agency to support or refute associations between the drug and the adverse event by using our novel method.

5.4 Future Research Directions:

It has been known that there are always a steady percentage of cases of various types of organ failure among the general population where the exact cause has not been determined. Constructing a database of the incidence of those organ failures, will have a tremendous utility in studies to detect any increase in their incidences. Collection of such data may help researchers and health care providers to have easier access to this epidemiological information and to use these data to identify earlier any suspicious increase in the incidence rate of these serious organ failures and relate them to a causative agents. The databases will also be useful to determine any association of certain adverse events with any newly marketed medicine.

We recommend an intensive follow up of any newly marketed drug where an effective reporting system is established to make sure that the story of pemoline will not be repeated.

CHAPTER SIX: CONCLUSION

Based on our analysis, there was sufficient evidence to conclude that pemoline was significantly associated with ALF in 1978 (four years after its introduction), rather than in 2000, when it was banned in Canada or 2005 in the U.S. Our study reveals that the published medical literature is a poor source for ADR reports, making it unreliable to test the association between pemoline and ALF. However, the published cases were a reliable source for conducting causality assessment, because they included most of the necessary details. In contrast, the FDA cases lacked detailed information, making it an impossible to make an effective causality assessment. Yet, the novelty of our method is not in proving causality, but rather, in early production of a signal that should lead to more in-depth assessment.

This method should enable researchers, clinicians, drug companies and regulators to identify uncommon adverse drug reactions, associated with new medications, earlier in the course of marketing and thus quantify serious ADRs and identify patient populations at special risk.

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