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[Jick H \(1977\)](#). The discovery of drug-induced illness. *New England Journal of Medicine* 296:481-485.

Key passages

SPECIAL ARTICLE

THE DISCOVERY OF DRUG-INDUCED ILLNESS

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Abstract The increased use of drugs (and the concurrent increased risks of drug-induced illness) require definition of relevant research areas and strategy. For established marketed drugs, research needs depend on the magnitudes of risk of an illness from a drug and the base-line risk. With the drug risk high and the base-line risk low, the problem surfaces in premarketing studies or through the epidemic that develops after marketing. If the drug adds slightly to a high base-line risk, the effect is undetectable. When

both risks are low, adverse effects can be discovered by chance, but systematic case-referent studies can speed discovery. If both risks are high, clinical trials and nonexperimental studies may be used. With both risks intermediate, systematic evaluations, especially case-referent studies, are needed. Newly marketed drugs should be routinely evaluated through compulsory registration and follow-up study of the earliest users. (*N Engl J Med* 296:481-485, 1977)

Table 1. Types of Drug-Illness Relations.

CATEGORY	RATE OF ILLNESS*		EXAMPLE	PRIMARY MODE OF DISCOVERY	RESEARCH APPROACH OF CHOICE		ILLNESSES OF PARTICULAR INTEREST
	DRUG INDUCED	BASE LINE			DRUGS ALREADY MARKETED	NEWLY MARKETED DRUGS	
1	High†	Low‡	Thalidomide-induced phocomelia	Clinical observation	Case referent	"Cohort"	Any rare illness
2	Low	High	—	Not discoverable	—	—	—
3	Low	Low	Chloramphenicol-induced aplastic anemia	1: Clinical observation 2: Formal research	Case referent	"Cohort"	Any rare illness
4	High	High	? Tolbutamide-induced cardiovascular mortality	Formal research	1: Clinical trial 2: Case referent 3: "Cohort"	1: Clinical trial 2: "Cohort"	Myocardial infarction & sudden deaths in high-risk populations
5	Intermediate	Intermediate	Estrogen-induced endometrial cancer	Formal research	Case referent	"Cohort"	Particular cancers

*Refers to acquired illness only.

†Arbitrarily defined as >1/200/yr for the purposes of this paper.

‡Arbitrarily defined as <1/10,000/yr for the purposes of this paper.