Developing Drug Literatures. 1. Bibliometrics of Baclofen and Dantrolene Sodium

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The literatures of two antispastic drugs, baclofen and dantrolene sodium, were studied bibliometrically for their first decade and were found to be generally similar. Baclofen had 93 papers and dantrolene sodium had 70. About a quarter of the baclofen papers were in a foreign language, whereas almost all dantrolene sodium papers were in English. Baclofen literature had a lower nonscholarly content, but the scholarly increase, 5%, was the same for both. Both drugs had an average of 12 references per paper. The literatures of both drugs had a similar degree of internal cohesiveness; almost half of their papers referred to other papers in the same drug collection. The first human paper for baclofen was the second published; for dantrolene sodium, it was the eleventh. The distribution of journals carrying papers on each of these drugs followed Bradford's law. Two authors per paper was the average for each drug. The productivity of authors approximated Lotka's law for both drugs. About two-thirds of the papers of both drugs had a drug-word in their titles. The literature of both drugs contained about 15% legendary papers, typical of clinical pharmacology. The most intense papers, 15 for baclofen and 11 for dantrolene sodium, were identified, using citation, bibliographic coupling, and co-citation frequencies. A generalization predicts what might be expected from the literature of future antispastic drugs.

INTRODUCTION

A literature—the body of writings on a subject—can be studied as a phenomenon in its own right. Bibliometrics, the statistical analysis of literature,[1] provides methods for such study.[2] Because the literature stands as a permanent historical record of the development of information, bibliometric investigations afford opportunities to compare, quantitatively, the evolutions of different literatures and, thereby, to uncover how information is used to generate new knowledge. More important, however, these comparisons can be analyzed to reveal certain generalizations which can be applied to similar literatures. Practical "laws" can be established which will enable those working with new or unfamilar literature to operate adroitly with only minimal familiarization.

The literatures of developing drugs are especially good models to study, because they start at a known point in time and continue to grow thereafter. Literature does not always mirror reality, and drug literature certainly does not; it has, in effect, a reality of its own independent of the actual events which it reports—all the more reason for studying it. For example, the usual sequence in the development of a drug is: chemical synthesis, animal studies, and administration to humans; the literature, on the other hand, is often just the opposite, the first paper published on a drug reporting its administration to humans, and the animal and chemical work appearing later.[3] It is hoped that further study of drug literatures will uncover other peculiarities.

The main points of interest in comparing two literatures are how information enters the literature, how it is transferred within the literature, and how the literature becomes structured. Each of these points can be quantified in terms of various measurable indicators: for example, the number of authors putting information into the literature, whether they are publishing alone or in groups, whether these groups are related or independent, the rate at which papers are being published, the number of papers actually being used to generate further papers. The quantitifications can then locate the ensembles of papers which are the most intense in their transfer of information—the active sites, as it were, within the overall structure of the literature.

In order to conduct such a comparative bibliometric study, virtually complete collections of the literatures being compared are required. Such collections were available for two recently marketed antispastic drugs, baclofen and dantrolene sodium. Baclofen is the generic name for β-(aminomethyl)-*p*-chlorohydrocinnamic acid, also known by its trade name, Lioresal® (Ciba-Geigy), and by its investigative code, Ba-34,647.[4] It is an analog of the putative neurotransmitter, GABA (γ-aminobutyric acid), being β-4-chlorophenyl-GABA (Table V: baclofen accession number 17). Dantrolene sodium is the generic name for 1-{[5-(*p*-nitrophenyl)furfurylidene]amino}hydantoin sodium salt hydrate, also known by its trade name, Dantrium® (Eaton), and by its investigative code, F-440.[5] Dantrolene itself, not the sodium salt, has an investigative code, F-368,[5] but does not have a trade name.

MATERIALS AND METHODS

Complete collections of both baclofen and dantrolene sodium publications were obtained using a five-pronged attack: (1) appropriate primary journals were scanned directly; (2) appropriate secondary journals were searched; (3) citation networks were traced[6]; (4) invisible colleges were deciphered[7]; (5) publication flow rates were analyzed. Each paper obtained was filed by an assigned accession number. An author file was established for cross-referencing. The citations in each paper were checked against the author file; those in the corresponding drug system were identified on the master document with their proper accession numbers. The citation accession numbers were, in effect, index terms for the document. Citation networks were then constructed using the accession numbers. Bibliographic coupling[8] and cocitation patterns[9] were investigated. The number of authors, the number of papers cited, and the number of pages were all counted for each paper. The language and the type of publication were recorded. Whether or not the titles contained baclofen or dantrolene words was also noted. The drug-words in titles and the legendary–

Table I. Basic Bibliometric Data for the Literatures of Baclofen and Dantrolene Sodium

	Baclofen	Dantrolene sodium
Total number of papers	93	70
Authors per paper		
Mean	2	2
Median	2	2
Mode	1	2
Range	1–7	1–6
Single-authored papers	38 (40.9%)	23 (33.9%)
Multi-authored papers	55 (59.1%)	47 (67.1%)
Pages per paper		
Mean	8	5
Median	4	3
Mode	1	1
Range	1–21	1–26
Languages		
English	70 (75.3%)	66 (94.3%)
French	5 (5.4%)	2 (2.9%)
German	8 (8.6%)	1 (1.4%)
Italian	4 (4.3%)	0
Japanese	2 (2.2%)	0
Spanish	2 (2.2%)	0
Dutch	1 (1.1%)	1 (1.4%)
Norwegian	1 (1.1%)	0
Type of publication		
Journal	71 (76.3%)	63 (90.0%)
Book	18 (19.4%)	1 (1.4%)
Patent	4 (4.3%)	5 (7.1%)
Newspaper	0	1 (1.4%)
Drug-word in title	60 (65.9%)	48 (68.6%)
Drug-word not in title	31 (34.1%)	22 (31.4%)
Papers with references	64 (76.2%)	42 (64.6%)
Papers without references	20 (23.8%)	23 (35.4%)
Legendary papers	13 (14.9%)	10 (15.4%)
Contemporary papers	74 (85.1%)	55 (84.6%)
References per paper (of those papers with at least one reference)		
Mean	12	12
Median	9	8
Mode	5	1
Range	1–40	1–42

contemporary determinations were measured by methods previously published.[10,11]

As both of these literatures are still growing at a healthy rate, a cut-off point had to be made in order to wrap up this study. This cut-off process was repeated several times, and no overall changes were apparent when the measuring was resumed. Therefore, it is felt that this study accurately reflects the state of these two literatures at this time. Furthermore, both of these literatures are already over 8 years old, so any additional papers in the next few months should not be expected to exert any significant change.

Some documents in these collections were not available for examination and could not be included in those studies where actual inspection was necessary, such as analyzing their references. Results expressed in percent were calculated as if these missing documents did not exist. These missing documents were not excluded from the entire study, however, because their citations still provided other valuable data, such as publication rates.

RESULTS

Basic bibliometric results are compared in Table I. Citation data are presented separately (Table II). Annual publication flow rates are given together with the annual change in rate and the cumulation (Table III); the growth curves are presented graphically (Figure 1), as are the annual changes of publication rates (Figure 2).

The journals in each drug collection were ranked according to the number of papers contributed (Table IV). Although there was no overlap at the top, near the bottom ten journals yielded papers for both drugs, three papers being the same for both drugs. Out of a total of 74 journals, this overlap amounted to 13.5%. The Bradford zones[12] are also

Table II. Citation Data within Each Drug Collection

	Baclofen	Dantrolene sodium
Papers never cited by another paper in the same drug collection	48 (51.6%)	38 (54.3%)
Papers cited at least once by another paper in the same drug collection	45 (48.4%)	32 (45.7%)

Frequencies of citation by other papers in the same drug collection

Times cited	Papers	Papers
29	1	0
22	1	0
20	2	0
16	0	1
15	1	0
14	1	0
13	1	2
12	0	2
11	0	1
10	0	1
9	0	1
8	1	0
7	0	2
6	2	1
5	2	0
4	2	1
3	4	4
2	9	8
1	18	8

Co-citation frequencies

Times co-cited	Pairs of papers	Pairs of papers
18	1	0
15	1	0
13	4	0
11	2	0
10	3	0
9	2	4
8	3	4
7	2	5
6	4	0
5	4	10

Bibliographic coupling frequencies

Times coupled		
9	0	1
8	0	1
7	0	3
6	6	8
5	29	6
4	44	17

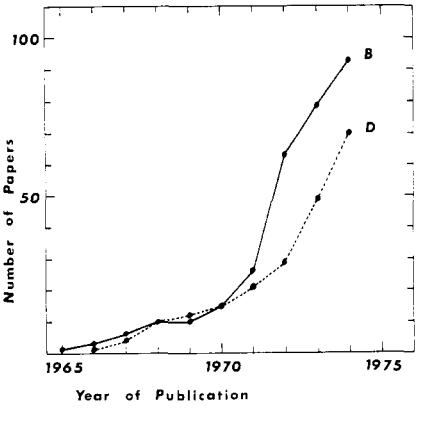

Figure 1. Growth of baclofen (solid line) and dantrolene sodium (dotted line) literatures.

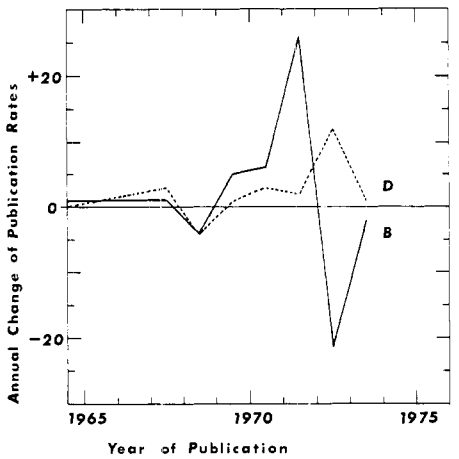

Figure 2. Annual changes of publication rates of baclofen (solid line) and dantrolene sodium (dotted line).

Table III. Publication Flow Rates

	Baclofen			Dantrolene sodium		
	Papers	Change	Cumulative papers	Papers	Change	Cumulative papers
1964	0		0	0		0
		+1			0	
1965	1		1	0		0
		+1			+1	
1966	2		3	1		1
		+1			+2	
1967	3		6	3		4
		+1			+3	
1968	4		10	6		10
		−4			−4	
1969	0		10	2		12
		+5			+1	
1970	5		15	3		15
		+6			+3	
1971	11		26	6		21
		+26			+2	
1972	37		63	8		29
		−21			+12	
1973	16		79	20		49
		−2			+1	
1974	14		93	21		70

given and, compared with the Bradford series of $1:n:n^2:n^3 \ldots$; the journal expansion series for baclofen was $1:3:3^{1.5}:3^{3.2}$ and for dantrolene sodium was $1:2:2^{1.6}:2^{2.8}:2^{4.2}$.

DISCUSSION

These bibliometric data reveal striking differences between the literatures of baclofen and dantrolene sodium, the most notable being that baclofen has 23 more papers than dantrolene sodium. However, 17 baclofen papers came from a book,[13] whereas none of the dantrolene sodium papers did. Each drug had a symposium published as an issue of a journal; in 1972 a supplement to *Postgraduate Medical Journal*[14] contained 12 papers on baclofen and in 1974 an issue of *Archives of Physical Medicine and Rehabilitation*[15] contained 7 papers on dantrolene sodium.

Another overt difference (Table I) between the two literatures is that about a quarter of the baclofen papers are in a foreign language; almost all of the dantrolene sodium papers are in English.

The scholarliness of a body of literature can be expressed by the equation $y = bx + a$, where y is the cumulative percent of papers, b is the scholarly increase, x is the number of references per paper, and a is the nonscholarly content.[16] Baclofen literature has a lower nonscholarly content (a = 23.8) than does dantrolene sodium (a = 35.4). However, the scholarly increase is the same (b = 5%) for the two

Table IV. Journals in Which Papers for the Drug Collections Were Published

Journals	Papers	%	Cumulative %	Bradford zone	Bradford series
Baclofen					
				–	–
Postgrad. Med. J.	12	16.9	16.9	1	1
Arch. Phys. Med. Rehab.	5	7.0	23.9	–	–
J. Neurol. Sci.	4	5.6	29.5	2	3
Lancet	4	5.6	35.1		
Unlist. Drugs	4	5.6	40.7	–	–
Acta Neurol. Scand.	3	4.2	44.9		
Brit. Med. J.	2	2.8	47.7	3	$3^{1.5}$
Med. Welt	2	2.8	50.5		
Riv. Neurol.	2	2.8	53.3	–	–
33 other journals	33	46.5	99.8	4	$3^{3.2}$
Totals	71			–	–
Dantrolene Sodium					
				–	–
Arch. Phys. Med. Rehab.	9	14.3	14.3	1	1
Fed. Proc.	7	11.1	25.4	–	–
J. Pharm. Sci.	4	6.3	31.7	2	2
J. Am. Med. Assoc.	4	6.3	38.0	–	–
Am. J. Phys. Med.	3	4.8	42.8		
Naunyn-Schmiedebergs' Arch. Pharmacol.	3	4.8	47.6	3	$2^{1.6}$
Acta Neurol. Scand.	2	3.2	50.8	–	–
Develop. Med. Child. Neurol.	2	3.2	54.0		
Med. World News	2	3.2	57.2		
Neurology	2	3.2	60.4	4	$2^{2.8}$
Pharmacologist	2	3.2	63.6		
South. Med. J.	2	3.2	66.8		
Touch	2	3.2	70.0	–	–
19 other journals	19	30.2	100.2	5	$2^{4.2}$
Totals	63	100.2		–	–

drugs. Furthermore, both drugs had the same mean number of references per paper (of those papers which had at least one reference), 12, and both had almost the same median: baclofen 9, dantrolene sodium 8. The ranges of references per paper were almost the same: baclofen 1 to 40, dantrolene sodium 1 to 42. The mode number of references per paper was 5 for baclofen and only 1 for dantrolene sodium; this difference reflects the type of paper written—whether an addition of another fact heaped upon a previous paper or an addition of information woven into previous literature.

The number of references per paper is a measure of scholarliness which, by its very nature, includes references to all and any literatures. An entirely different measure is the number of references per paper only to other papers in the same collection, which is a measure of the internal cohesiveness of a literature. In this attribute both drugs have a very similar score: baclofen 48%, dantrolene sodium 46% (Table II).

The bibliographic coupling and co-citation data (Table II) seem to be diametrically opposite for the two drugs; baclofen has some high-frequency co-citations with low-frequency bibliographic coupling, whereas dantrolene sodium is just the reverse. Garfield[17] has pointed out that co-citation is the mirror image of bibliographic coupling, and perhaps this drug comparison is just a fortuitous example. Papers which are co-cited or bibliographically coupled are, in effect, bonded together; the strength of this bond can be measured, to some extent, by the frequency with which they are bonded. Clusters of papers bonded together by high frequencies of co-citation or bibliographic coupling represent the sites of the most intense activity in the structure of a literature. The papers which make up these clusters are therefore the fundamental building blocks of the literature and must be identified in order to understand how information reverberates within the formal publication matrix. That is, in order to isolate the points at which information flows through a mere collection of papers, it is necessary to single out those papers which are linked to each other by information bonds, bonds which the rest of

Table V. The Most Intense Papers in the Drug Collections, as Determined by the Intensities of Their Information Bonds

	Baclofen	Dantrolene sodium
Most frequently cited papers	8 (29×)	2 (16×)
	17 (22×)	11 (13×)
	13 (20×)	14 (13×)
	24 (20×)	8 (12×)
	21 (15×)	9 (12×)
	46 (14×)	18 (11×)
Most frequently bibliographically coupled papers	53 to 73 (6×)	49 to 54 (9×)
	53 to 78 (6×)	19 to 54 (8×)
	53 to 83 (6×)	19 to 49 (7×)
	67 to 76 (6×)	54 to 63 (7×)
	71 to 75 (6×)	54 to 66 (7×)
	73 to 78 (6×)	
Most frequently co-cited papers	8 + 24 (18×)	8 + 11 (9×)
	8 + 17 (15×)	11 + 12 (9×)
	8 + 13 (13×)	11 + 14 (9×)
	8 + 21 (13×)	12 + 14 (9×)
	12 + 13 (13×)	2 + 8 (8×)
	13 + 17 (13×)	2 + 11 (8×)
	17 + 24 (11×)	2 + 14 (8×)
	17 + 46 (11×)	8 + 14 (8×)

Baclofen

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Balcofen (cont.)

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Dantrolene Sodium

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63 Ellis, K. O., and Carpenter, J. F., "Mechanism of Control of Skeletal-Muscle Contraction by Dantrolene Sodium", *Arch. Phys. Med. Rehabil.*, **55**, 362–369 (1974)

66 Ladd, H., Oist, C., and Jonsson, B., "The Effect of Dantrium® on Spasticity in Multiple Sclerosis", *Acta Neurol. Scand.*, **50**, 397–408 (1974)

the papers lack. The three main bonding types (from weakest to strongest)—citations, bibliographic coupling, and cocitations—are presented in Table V, symbolized by their drug information system accession numbers; the full citations of the papers are also given. These papers are, therefore, the most intense.

The first report of a drug's administration to a human is often the first paper published on that drug.[3] The first human paper for baclofen was by Bergamini et al. (Table V, baclofen accession number 21) and bears the publication date August 18, 1966. It was the second paper published on baclofen, the first being a patent (CIBA, Netherlands 6,407,755, January 11, 1965). The first human paper for dantrolene sodium was by Cox et al.[18] and bears the publication date August 1969. It was the eleventh paper published on this drug, the others being three announcements, five patents, and two chemical papers. The Bergamini paper was a clinical trial; the first comparable clinical-trial paper for dantrolene sodium was by Chyatte (Table V, dantrolene sodium accession number 9) and bore the date February 1971; it was the sixteenth dantrolene sodium paper and the fourth human paper. Therefore, with regard to the first-human-paper concept, baclofen is typical and dantrolene sodium is atypical.

The small overlap of journals carrying papers on these two drugs (Table IV) conveys a practical lesson for designers of scanning operations for monitoring literature on developing drugs. The ensemble of journals that is adequate for one drug may be quite inadequate for another, even a similar, drug. However, although the actual journals involved may be dissimilar, the kinetics of publication within journals is very similar. Bradford's law[12] states that when all the journals in which papers on a subject appeared are ranked in order of their yield, the number of papers produced by the top journal will be produced by n journals, and then by n^2 journals, and then by n^3 journals, and so on. Each repeat of the initial yield of papers is called a zone. The Bradford zones for baclofen and dantrolene sodium

TABLE VI. Author Productivity

No. of papers per author	% of all authors		
	Lotka's law	Baclofen	Dantrolene sodium
1	60	67	64
2	15	24	21
3	7	5	9
4	4	4	3
5	2	0	1
6	2	0	1
7	1	0	0
8	1	0	1

are given in Table IV. The exponents follow, roughly, the Bradford series.

The number of authors per paper is a measure of the social conditions surrounding the publication of information on a particular subject. Both drugs have almost identical author measures (Table I), the only difference being that the mode for baclofen is 1 and for dantrolene sodium 2. A more fundamental difference, not evident from the tables, is the frequency with which the same authors appear. For baclofen, the most papers by any one author is four, with five authors achieving this number. For dantrolene sodium, one author (Ellis) published eight papers, all co-authored; one author published five, and two published four papers each. As most papers had multiple authors (Table I), neither literature was dominated by solitary authors. In fact, of the most intense papers listed in Table V, all but one are multiauthored.

Lotka's law is a measure of author productivity which states that about 60% of all the authors, in a given field, publish only one paper in that field and the number of authors publishing n papers is about $1/n^2$ of those publishing one paper.[19] Or, restated simply, the percent of authors publishing n papers is $60\%/n^2$. Lotka formulated his law after examining almost 7000 authors. Expecting it to apply to small populations of authors may be risky. However, identifying the most productive authors is very important in monitoring developing drug literatures. The author productivities for each drug literature are listed in Table VI, along with the Lotka values.

The literatures of both drugs had almost the same percent of drug-words[10] in their titles, baclofen with 66% and dantrolene sodium with 69% (Table I). These percentages are very close to the 71% reported for DOPA[10] and confirm the practical utility of monitoring developing drug literatures by the use of title-oriented secondary journals.

Both baclofen and dantrolene sodium have low percentages of legendary papers, about 15% (Table I). This is a characteristic of clinical pharmacology, 13.5%, as opposed to general pharmacology, 44.9%, based on an assay of the 1972 issues of *Clinical Pharmacology and Therapeutics* (Volume 13) and *The Journal of Pharmacology and Experimental Therapeutics* (Volumes 180–183), respectively, using the method previously published.[11]

The differences in the literatures of these two drugs are relatively minor compared to the general similarities. The fact that these two drugs were discovered and developed independently and yet established similar literature structures indicates that the literature characteristics are not as dependent on the drugs as chemical entities as they are on the drugs as a therapeutic class. That is, other antispastic drugs will probably also develop literature structures similar to those described here. Comparisons of literature structures of drugs from different therapeutic classes will have to be done in future studies.

In generalizing from the investigation of these two drugs, a new antispastic agent might be expected to generate about 80 papers in its first decade, 50 of which would appear in the seventh to tenth years. Most papers would be in English, multiauthored, and about six pages long, and would have about 12 references per paper; they would appear in journals following a Bradford distribution, would have the drug word in the title, and would be contemporary. A considerable degree of internal cohesiveness would exist and ensembles of intense papers would be established.

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