Trends in Pharmacological Sciences

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REVIEWS

Opinion

What Can Big Data on Academic Interest Reveal about a Drug? Reflections in Three Major US Databases

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The different stages of the life cycle of a drug – 'prenatal' stage, birth of a drug, rapid growth, maturity and stability, decline, and status before 'death' – are reflected in the three following databases: journal articles (PubMed—www.ncbi.nlm.nih.gov/pubmed); patents (US Patent Office—http://partfl1.uspto.gov/netahtml/PTO/search-adv.htlm); and approved drugs (FDA – www.accessdata.fda.gov/scripts/cder/drugsatfda/index/cfm). These databases are huge, from authoritative sources, correctly classified, and they properly link different datasets. Analysis of such data can uncover hidden patterns important for the assessment of drug status and may also yield some predictions regarding its future prospects. Drug-related, publication-based academic bibliographic records are especially numerous and support the development of various scientometric indices. In combination with information from other types of databases, they can outline various trends in pharmacology. Scientometric indices can be classified into those indicating a change in the status of a drug, and those assessing the chances for success, or even drug discontinuation. Here, we present big data analytics on publication-based academic interest in two segments: (i) description of scientometric indices and (ii) their applications for the assessment of the status of a drug.

Highlights

Drug-related academic interest is reflected in the databases compiled from biomedical journal articles. The PubMed bibliographic records in combination with the records in two other databases – on patents (database of US Patent Office) and on approved drugs (database of FDA) – provide important information for big data analytics to outline various trends in the evolution of drug status.

Drug-related records on publication-based academic interest were used to develop the following scientometric indices: PI, TJSI, IC, IUS, and TBI.

The scientometric indices can serve as the initial signs of significant new drug-related development (patent-related PI, TBI, TJSI, and IC), the evidence of drug success (IUS, long-lasting rise in PI, and TJSI), or signs of possible market discontinuation (low PI).

Description of Scientometric Indices

There have been multiple suggestions that publication-based indices can be used to show potentially fruitful areas for drug discovery, based on the assumption that higher levels of scientific activity, including publication rates, can point to specific targets for novel therapies [1]. The first attempt to predict the clinical success of drugs using bibliometric data was made by Windsor in 1976 [2], who wrote: 'Just as rabbits leave rabbit tracks and squirrels leave squirrel tracks – successful drugs leave different bibliometric tracks than do unsuccessful drugs. Sometimes these track records can be used to make predictions'. He used bibliometric traits of the journal literature on the anti-Parkinson drug levodopa over a 14-year period to identify predictors of success of the drug [3]. He concluded that the bibliometry of single-author papers may have promise in this regard. In 2011 a scientometric indicator, the **Top Journal Selectivity Index** (TJSI) (see Glossary), was suggested for use in the assessment of therapeutic drugs [4,5]. Since then, several additional scientometric indices have been suggested [6–9]. These indices summarize the previous efforts to monitor the status of drugs and drug candidates at different stages of their life cycle ('prenatal stage', growth, maturity, decline, and status before 'death'), as well as to assess their possible fate. Here is a brief summary.

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Popularity Index

The **Popularity Index** (PI) is the percentage of articles on a specific topic among all articles in the related area published over the same period (usually 5 years), that is, comparative popularity [7,9]. Publication-based academic interest related to drugs can be analyzed using big data extracted from the databases of biomedical publications. The PubMed database of the US National Library of Medicine provides the best information for determining PI. This database is large, with >27 million citations in biology and medicine, it is from an authoritative source, and most importantly, it has a reliable controlled vocabulary for indexing articles – Medical Subject Heading (MeSH) terms. PI includes all types of articles in all journals covered by PubMed. There is a constant growth in numbers of PubMed drug-related articles in all medicobiological areas. On average, growth is in the range of 20–30% per 5-year period, but it varies in different areas; the PI allows the measurement of comparative popularity. The PI was calculated as the ratio (expressed in percent) of the number of articles on a specific topic that might be a particular drug (e.g., sumatriptan) among articles on a related area (in this case – all articles related to migraine disorders). Similarly, a specific topic might be bupivacaine and a related area – all articles on regional anesthesia. If the PI on a specific topic increases compared to its related area, it means that the popularity of the topic is growing. For a detailed description of the methodology, see [7,9]. Figure 1 gives several examples of changes in three indices, including PI. The most dramatic increase in PI occurred with bupivacaine in the area of regional anesthesia (Figure 1A).

Similarly, the patent-related PI is the percentage of patents on a topic among all US patents pertinent to a comparative field (such as patents on serotonin and pain among all patents on pain, Figure 2A) [8].

TJSI

The TJSI is the ratio of the number of articles on a particular topic in the top 20 journals relative to the number of articles on the same topic in all (>5000) biomedical journals covered by PubMed over a 5-year period [4,5,9]. The topic includes both a drug and its specific area of administration. To determine TJSI, the 20 top journals are selected based on two factors: (i) their rank sorted by impact factor, as indicated by Journal Citation Reports; and (ii) the specialty area of the journal related to the specific drug group or pharmacological class. Half of the journals represent general biomedical interest, such as *Science*, *Nature*, *New England Journal of Medicine*, *Journal of the American Medical Association (JAMA)*, and *The Lancet*. The other half represent specialty journals and journals covering neighboring specialties; for example, for local anesthetics, those might be *Anesthesiology*, *Pain*, *Annals of Surgery*, and *Journal of Pharmacology and Experimental Therapeutics*. The TJSI represents the level of interest in select top journals and indicates when the excitement regarding a specific topic begins to spread into neighboring areas. This index can be regarded as an indication of expectations at the time of articles publication; it is usually the first among scientometric indices to indicate promising development. The TJSI was calculated as the ratio (expressed in percent) of the number of articles on a topic in the top 20 journals relative to the number of articles on this topic in all journals covered by PubMed. For a detailed description of the methodology, see [4,5,9].

In the assessment of the success of new drugs over the past 50 years, we observed a difference in the publication response to a new drug between biomedical journals in general and in the top journals: the number of published articles on a drug changed (either increased or declined) more rapidly in the top journals. This observation prompted the introduction of TJSI as an early indicator of drug success [4,5]. This aspect of TJSI can probably be explained by the

Glossary

Index of Change (IC): change (%) in the number of articles on a topic during a time period compared to the number of articles on the same topic published during a previous period of the same length. The IC reflects the degree of change in interest in a topic, irrespective of the changes in the related field.

Index of Ultimate Success (IUS): degree (%) of decline in the PI of supplanted drug due to the use of a new drug for the same purpose. A decline in the PI of a supplanted drug by ≥50% during an interval of 10–20 years, is a sign of major success for the new drug.

Popularity Index (PI): percentage of articles on a specific topic among all articles in the related area published over the same time period. The PI measures the topic popularity among the authors of publications in a specific area, i.e., specific comparative popularity.

Top Journal Selectivity Index (TJSI): ratio (%) of the number of articles on a particular topic in the top 20 journals relative to the number of articles on the same topic in all (>5000) biomedical journals covered by PubMed. TJSI represents the level of interest in the selected top journals; usually it is the first index to indicate a promising development.

Trial balance index (TBI): ratio (%) of the number of articles reporting the Phase I plus Phase II trials of new investigational drugs on a topic versus the number of articles reporting Phase III trials on the same topic. The TBI indicates whether the interest in the development of a target is at its beginning or end.

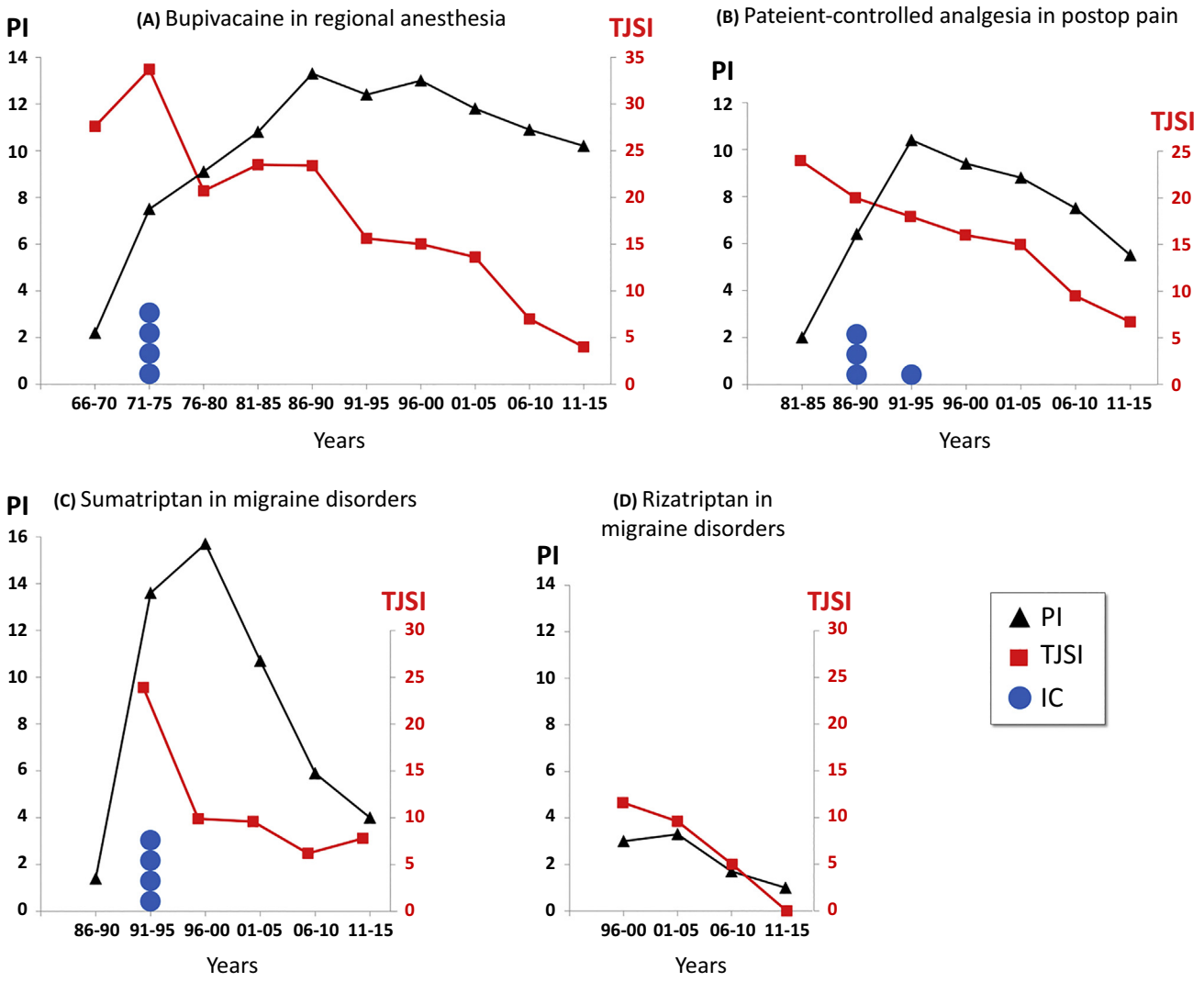

Figure 1. Time Courses of Three Specific Indices (PI, TJSI, and IC) Reflecting Publication-Based Academic Interest in Various Drug-Related Applications. (A) Bupivacaine in regional anesthesia. (B) Patient-controlled analgesia in postoperative pain. (C) Sumatriptan in migraine disorders. (D) Rizitriptan in migraine disorders. Abbreviations: IC, Index of Change, representing the change (%) in the number of articles on a topic during a 5-year period compared to the previous 5-year period. The circles represent the degree of change: one circle, ≥100%; two circles, ≥200%; three circles, ≥300%; four circles, ≥400%. PI, Popularity Index representing the number of articles on a topic as a percentage of all articles in a field (regional anesthesia in A, postoperative pain in B, migraine disorders in C and D). TJSI, top journal selectivity index representing the ratio (%) of the number of articles on a topic in the top 20 journals relative to the number of articles on the same topic in all (>5000) biomedical journals covered by PubMed. Adapted from [4,17].

high-caliber experts involved in the assessment of manuscripts evaluating new drugs in the top journals. When we used the top 100 journals instead of the top 20, the differences in TJSI values were not distinct. However, the duration of assessment periods can be changed; for example, the assessment period could be decreased to 3 years if the increase in the rate of publications in all journals is sufficiently high from the very beginning. Examples of TJSI are presented in Figure 1.

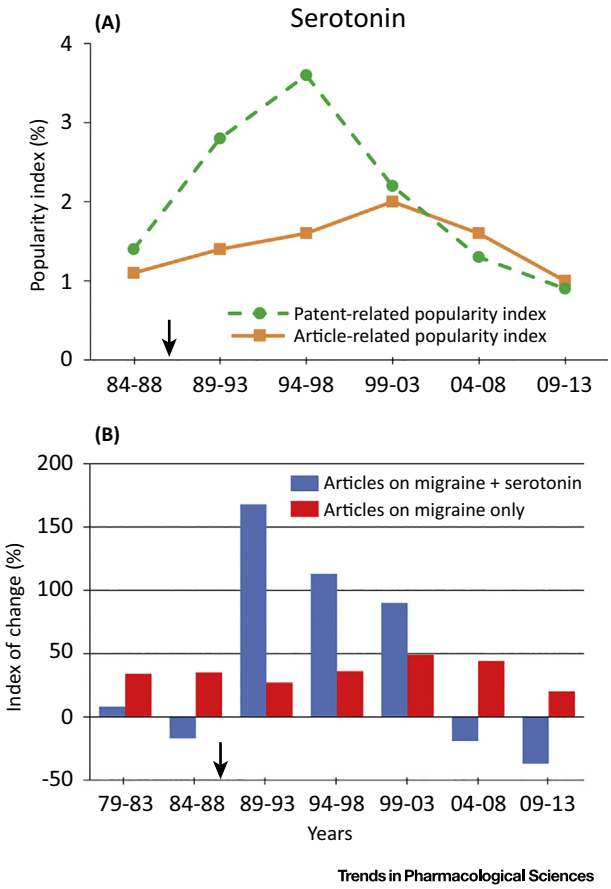

Figure 2. Time Courses of Indices (PI and IC) Associated with Serotonin-Related Discovery of Sumatriptan – a Novel Drug for Treatment of Migraine. (A) Comparison of patent-related and journal-article-related PIs. (B) Comparison of IC for articles on migraine and serotonin in combination versus articles on migraine only. The arrow indicates the publication time of the first article on sumatriptan [11,12]. Abbreviations: IC, Index of Change; PI, Popularity Index. Adapted from [7,8].

Index of Change

The **Index of Change** (IC) reflects the change in the number of publications on a topic during a 5-year period compared to the previous 5-year period. It is calculated as the percentage change in the number of articles on a particular topic between the two periods: the difference between these periods is divided by the original number and multiplied by 100. For a detailed description of the methodology, see [7]. The IC represents the degree of change in interest in that topic irrespective of changes in the related area, it measures the speed of growth in publications on a topic. The specific high threshold used for this index was usually set at ≥100% growth, because changes in this index are variable. The IC usually exceeds this high threshold during the 5-year period following a large rise in the TJSI.

Index of Ultimate Success

The **Index of Ultimate Success** (IUS) is a publication outcome indicating that a new drug (or a group of drugs) has replaced a drug previously commonly used for the same purpose. It is measured by the degree of decline in the PI of a supplanted drug; for example, a decline of ≥50% over 10–20 years is interpreted as representing a positive IUS. For a detailed description

Table 1. IUS: new drug success, expressed as degree of decline in PI of an old drug used for the same purpose

New family of drugs		Disorder or disease	Old (supplanted) drugs	Decline of PI of supplanted drugs at different time intervals (years since new drug introduction)				
Group name (first drug)	Year of first drug approval			(5)	(10)	(15)	(20)	(25)
PPIs (omeprazole)	1990	Gastroesophageal reflux	Histamine H_2 antagonists	32%	55%	71%	–	–
Triptans (sumatriptan)	1992	Migrane disorders	Ergotamine or Dihydroergotamine	15%	45%	67%	73%	–
Triazoles (itraconazole)	1994 (1984)	Mycoses	Imidazoles	32%	42%	45%	55%	–

of the methodology, see [7]. Table 1 shows changes in the popularity of competing drugs (new versus old) used in three different fields of pharmacotherapy (gastroesophageal reflux, migraine disorder, and mycoses). For example, Table 1 indicates that proton-pump inhibitors (PPIs) supplanted histamine H_2 inhibitors, offering a more effective and completely new mechanism of action with a new molecular target. As a result, by 2009–2013, the PI of the supplanted drugs – H_2 antagonists declined by ~70%.

Trial Balance Index

The **Trial Balance Index** (TBI) reflects the balance between the numbers of articles representing different phases of clinical trials of new investigational drugs: the ratio of the number of articles reporting Phase I plus Phase II trials on a topic versus the number of articles reporting Phase III trials on the same topic [8]. Clinical trials of a new investigational drug begin with Phases I and II, and if the results are promising, then the assessment proceeds to Phase III, in which safety and efficacy are studied in a large sample of selected patients. Usually several compounds offered by different companies but acting on the same molecular target undergo clinical trials roughly simultaneously. Initially, articles representing trials of new investigational drugs are limited to Phases I and II; later articles on Phase III trials began to appear and their numbers increase rapidly. The research efforts of the pharmaceutical industry related to a new molecular target are reflected by the total number of new Phase I–III clinical trials. The balance between phases of trials (TBI) indicates whether interest in the development of a target is at its beginning or end. For a detailed description of this methodology, see [8]. In 2009–2013, the TBI for clinical trials of all investigational drugs covered by PubMed was 2.8. The newer the molecular target at the center of industry interest, the higher the ratio, and vice versa. Table 2 indicates that the TBI in the area of investigational drugs for pain relief in 2009–2013 was lower than this average (2.8).

Scope of Indices Applications

These indices (PI, TJSI, IC, IUS, and TBI) allow us to assess different aspects of publication-based academic interest. Assessments of various pharmacological targets may include molecular targets (such as serotonin-related targets, Figure 2A), investigational drugs, individual approved drugs (such as bupivacaine, Figure 1A), a specific group of drugs, an entire class of drugs, or a method of drug administration (such as patient-controlled analgesia, Figure 1B). The PI of a drug can be measured as it is related to a specific area of application and, as a result, can be applied in a number of ways. It can be presented (i) as the percentage of articles relative to a whole class of drugs (general PI); (ii) as a percentage of articles in a particular area, such as a specific disorder (specific PI), for example, sumatriptan in migraine disorders (Figure 1C); (iii) as a percentage of articles relative to a specific type of treatment, such as tetracaine among articles on spinal anesthesia (Figure 4A); or (iv) as a percentage of articles on a

Table 2. TBI: balance between Phase I–II trials and Phase III trial articles among investigational drugs for pain relief (2009–2013)

Area		No. of articles		TBI (I–II/III ratio)[a]
		Phase I–II	Phase III	
Drugs designed for pain relief	GABA	4[b]	13[b]	0.3
	Serotonin	7[b]	5[b]	1.4
Some other types of drugs[c]	Cytokines	1,070	303	3.5
	Protein kinases	1,233	256	4.8

GABA, γ-aminobutyric acid.
[a]TBI is a ratio of the number of articles representing the Phase I plus the Phase II trials of investigational drugs on a topic to the number of articles representing Phase III trials on the same topic [8].
[b]Only articles when pain was a primary aim of a trial.
[c]Not necessarily related to pain.

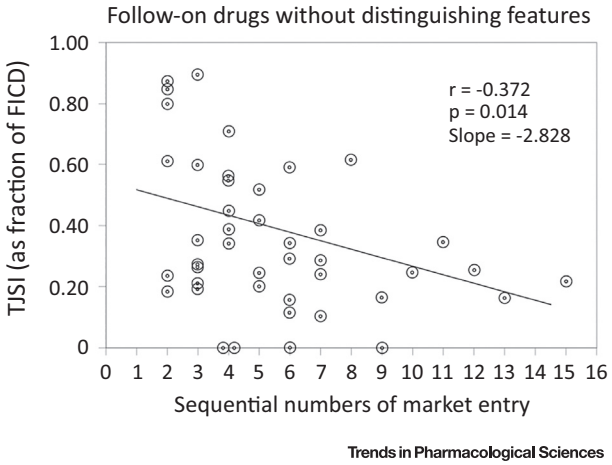

Figure 3. Relationship between TJSI of Follow-on Drugs without Distinguishing Features ('Me-Too' Drugs) and the Order (Sequential Number) of Market Entry of Drugs. TJSI presented as a fraction of FICD, calculated for each class separately. Sequential number of market entry for follow-on drugs starting with number 2 (number 1 is reserved for FICD). Circles indicate various follow-on drugs without distinguishing features (43 drugs). Abbreviations: FICD, first-in-class drug; TJSI, Top Journal Selectivity Index. Adapted from [6].

method of drug administration among articles on a specific general pathology, such as patient-controlled analgesia among all articles on postoperative pain (Figure 1B). These separate analyses can tell different things about the drug in question. For example, the PI of the same drug can indicate its popularity in general, as a drug used for the treatment in all possible clinical situations, or selectively for one specific disorder.

Scientometric Indices as Indicators of Drug Status

Analysis of scientometric indices can be used to assess the status and prospects of a drug. This is possible because they reflect the typical long-term profile of academic interest in a drug: a slow increase followed by a decline, each lasting 15–30 years. Changes in scientometric indices during this long period can reveal common signs of success or failure of a drug.

However, it is important to admit what scientometric indices cannot do: they cannot predict a transformative discovery ignited by a novel idea. An illustration comes from the scientometric records related to sumatriptan – the only novel and successful drug of 59 analgesics developed

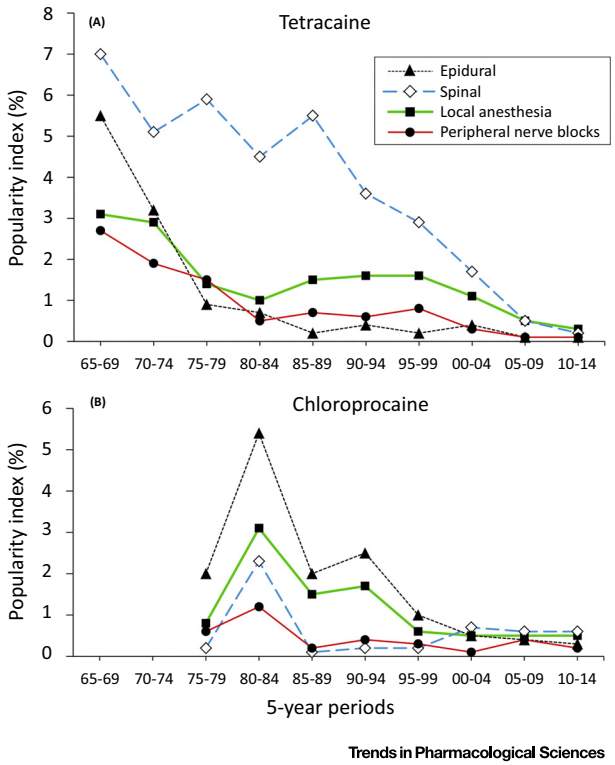

Figure 4. Time Course of PI for Tetracaine and Chloroprocaine in Various Forms of Regional Anesthesia. PI is the percentage of articles on tetracaine (A) or chloroprocaine (B) among all articles related to one of the specific forms of regional anesthesia: epidural, spinal, local, and peripheral nerve blocks. Abbreviation: PI, Popularity Index. Adapted from [14].

over the past 50 years (1960–2009) [10]. Figure 2B represents the degree of change in the number of articles on migraine in general and in the number of articles on migraine and serotonin in combination (a combined topic that culminated in the creation of sumatriptan) [11,12]. It is of interest that for two 5-year periods before the first publications on sumatriptan (1979–1983 and 1984–1988) there were no increases in the number of serotonin-related articles on migraine (in contrast to increases in publications on migraine in general). In addition, there was no increase in the patent-related PI on pain associated with serotonin. Thus, there were no discovery predictors based on increased publishing activity. However, after the first publications on sumatriptan, the number of articles on this topic increased dramatically, resulting mostly from the introduction of very similar drugs: various triptans.

Although scientometric indices cannot predict a transformative discovery, they can indicate the main direction of research efforts (and the flow of capital) that results in the creation of new drugs and new therapeutic applications that usually are not transformative, but represent progress. Here is what scientometric indices can signify regarding drug status and possible prospects.

Initial Signs of New Development

Patent-Related PI

Initial signs that may indicate an important development include the rise in patenting activity as seen in Figure 2A, reflecting serotonin-related patents. The patent-related PI grew faster than the article-related PI. In addition to potentially more rapid indication of the interest in a drug, the

patent-related PI may have an extra aspect. In contrast to the articles in academic journals, patents are filed because economic return is expected.

TBI

It represents another initial sign of new development indicating that interest in the development of a target is at its beginning or end. When the TBI for an investigational drug is high, it indicates the prevalence Phase I–II studies over Phase III studies, showing that a new development is in its initial stages (Table 2).

TJSI

It can be the most important initial indicator of a successful development: the higher the score, the greater the possibility of continuing success of a drug. Figure 1A indicates that the TJSI of bupivacaine in regional anesthesia was high (28) in the initial period (1966–1970), presaging high PI for almost 50 years. By contrast, rizatriptan (probably the most successful of the rest of the six triptans that followed sumatriptan) had an initial TJSI value of only 12, and its PI rapidly declined (Figure 1D).

IC

A large increase in the IC of a drug can also be a sign of important development, especially if it exceeds 100%. Such changes usually occur during the 5-year period following a large rise in the TJSI. For example, with bupivacaine in regional anesthesia, such an increase was more than 400% (1971–1975, Figure 1A).

Reliable Evidence of Success

IUS

IUS is the most reliable index of success, indicating that the introduction of a new drug has led to a decline in the number of articles on a drug formerly dominant for the same purpose. Table 1 gives an illustration of how PPIs supplanted histamine H_2 inhibitors in the treatment of gastroesophageal reflux.

Long-lasting rise in PI and TJSI

Other reliable evidence of the success of a drug is a long period of high values in both PI and TJSI. For example, patient-controlled analgesia had a high PI index for six 5-year periods, and high TJSI for five periods (Figure 1B).

Index for 'Me-Too' Drugs

Usually the introduction of a first-in-class drug (FICD) is followed by the development of many similar drugs, referred to as follow-on drugs (FODs). While some FODs have pharmacological properties that distinguish them from the FICD, others do not. Drugs without distinguishing features are often called me-too drugs, because they offer no significant benefits (including safety) over the previous agents [13]. It was shown that TJSI can help assess late market entrants that offer no real distinguishing features [6]. The analysis of FODs without distinguishing properties demonstrates (Figure 3) that the relationship between TJSIs for FODs and the order of the market entry of the drugs had a negative correlation ($r = -0.372$; $P = 0.014$): the higher the order (sequential number), the lower the TJSI. As a result, if the TJSI of an FOD is <0.5 of an FICD (expressed as a fraction of the TJSI of a FICD, calculated separately for each class of a drug), and market entry order is ≥ 5, the FOD is a me-too drug (with false-negative rate of only 9.1%) [6]. The FICD and the first three FODs that followed it were excluded from this analysis to eliminate the possibility of counting as me-too drugs those that might be involved in the process of competition for becoming the first drug in a new class.

Signs of Possible Market Discontinuation

Low PI

It is reasonable to assume that drugs with very low academic publication-based indices are more likely to be discontinued by the pharmaceutical industry than those in good standing. The present availability of local anesthetics in the United States is a good illustration [14]. However, strictly economic factors, such as profit margins and market shares, must play a decisive role. In general, it is possible to say that the unavailability of a drug for clinical use is usually preceded by long and profound declines in indices reflecting academic interest. Tetracaine is probably the most impressive example. Figure 4A shows that, the initial PI of tetracaine for spinal anesthesia was much higher than that of any other form of regional anesthesia. This situation persisted for more than 20 years, until 1985–1989. Tetracaine was rarely used for other forms of regional anesthesia because of its extremely slow onset of action and its potential for systemic toxic reactions [15]. After 1985–1989, the decline in PI of tetracaine was especially steep; and in 2005–2009, tetracaine PI values were low even with spinal anesthesia (Figure 4A). The inevitable result: the drug is no longer on the FDA list for injectable forms.

By contrast, the chloroprocaine PI values also profoundly declined, even with spinal anesthesia (Figure 4B). At the same time, since three pharmaceutical companies offer this drug in the US [14], the demand must be sufficient to drive some competition. Chloroprocaine [14] has a unique position among local anesthetics due to its short duration of action. This is probably the most important reason hospitals pay a higher price [16].

This Opinion represents work in progress toward the development of various indices to monitor the status of drugs and drug candidates as well as to predict their possible fate. Further progress in this direction could widen the scope of the analysis in various ways: by including new databases that reflect experiences of different countries or by adding various types of intellectual property documents with public or private drug-related information. The most important field for additional investigation is related to clinical trial databases, such as the US National Library of Medicine – clinicaltrials.gov, or the World Health Organization International Clinical Trial Registry Platform – www.who.int/trialsearch. The depth of publication-based analysis could be increased in many aspects. For example, the difference between the impact of patent-related documents and that of articles in scientific journals could provide an avenue for new investigation, since they measure very different intents: while scientific papers are written out of scientific interest, patents are filed for economic return. Only a multifaceted approach to the assessment of various databases reflecting academic drug-related interest can provide a reliable outcome.

Concluding Remarks

Drug-related publication-based academic interest is reflected in databases compiled from biomedical journal articles. The PubMed bibliographic records in combination with the records in two other databases – on patents (database of US Patent Office) and on approved drugs (database of FDA) – provide important information for big data analytics to outline various trends in the evolution of drug status. Drug-related records on publication-based academic interest were used to develop the following scientometric indices: PI, TJSI, IC, IUS, and TBI. They allow us to assess different aspects of publication-based academic interest. The scope of their applications can be an individual drug, a group of drugs, an entire class of drugs, or a method of drug administration. The relation of their applications can also vary: they can be presented relative to a whole class of drugs or to only one segment of pharmacotherapy, that is, a percentage of articles relative to the treatment of a specific disorder. These indices can serve as the initial signs of a significant new drug-related development (patent-related PI, TBI, TJSI, and

IC), the evidence of a drug's success (IUS, long-lasting rise in PI, and TJSI), or the sign of possible market discontinuation (low PI). Taken together, they provide a new framework for drug assessment. Assessment of drugs via scientometric indices should be combined with the evaluation of their effectiveness based on good-quality evidence obtained in randomized controlled trials and presented in meta-analyses. Only the combined assessment can offer a reliable representation of advancement in drug research. Big data on publication-based academic interest can be used far beyond the field of pharmacology. Some of the indices – PI, TJSI, and IC – can also be used in any research field (see Outstanding Questions).

Outstanding Questions

Can citation analysis be used for the assessment of academic interest in a drug?

How can the depth of publication-based drug assessment be increased by analysis of the difference between the impact of patent-related documents and that of articles in scientific journals? These two types of approaches measure different intents: while scientific papers are written out of scientific interest, patents are filed for economic return.

Can the drug-related publication-based interest assessment approach be applied to research fields not related to drugs? Three of the indices described here (PI, TJSI, and IC) can probably be used in any research field, that is, in disease categories – genetic therapy in sickle cell disease.

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