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Financial Conflict of Interest in Clinical Psychiatry Studies: A Review

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Abstract

Pharmaceutical industry revenues from global pharmaceutical sales have increased 7% to $602 billion in 2005. Approximately 15% of these revenues were spent on clinical research and drug development studies. Because of the huge budget allocated to research and development studies the number of studies being conducted by pharmaceutical companies has increased. The impact of the pharmaceutical industry on clinical trials has been affected by financial conflicts of interest between researchers and the industry.

Conflict of interest refers to a situation in which it appears that a researcher's personal financial interest could significantly affect the design, conduct, and/or reporting of such research. Financial conflict of interest has been reported to be frequent in clinical trials in general medicine. It is estimated that 89%-98% of comparative drug treatment studies are funded by pharmaceutical companies. It was reported that favorable outcomes for the firms conducting these studies were significantly more common in industry-funded studies than in non-industry funded ones. These biased outcomes were due to conscious or unconscious decisions about the design, data analysis, and publishing of the studies.

Biased outcomes of industry-funded studies have diminished the integrity of academic institutions, pharmaceutical companies, researchers, and scientific journals; therefore, various precautions have been taken in order to reduce the effect of conflict of interest on study outcomes. The aim of this review was to evaluate the effect of conflict of interest on outcomes in clinical psychiatry studies.

Key Words: *Conflict of interest, drug industry, psychiatry, psychopharmacology, bias*

INTRODUCTION

International Marketing Services (IMS) conducts marketing research about the pharmaceutical industry, total income the industry obtains from drug sales increases every year. By the year 2005 total income reached $602 billion, a 7% increase from the previous year. When we look at the regional distribution of the income obtained from worldwide drug sales, North America ranks first with $265.7 billion, followed by Europe with $169.5 billion, and Japan with $60.3 billion (Van Amum, 2006). The pharmaceutical industry devotes an important portion of this income to investigative and developmental studies in order to maintain a consistent increase in the total income and benefit rates. This accounts for approximately 15% of the total income obtained from drug sales (Bushfield, 2003). The drug industry's budget devoted to investigative studies began to increase after enactment of the "Patent and Commercial Brand Law" (PL 96-517) in the USA in 1980, which is known as Bayh-Dole. While the total budget allocated by pharmaceutical companies for investigative studies was $1.5 billion in 1980, it increased to $22 billion in 2001. With this law, which facilitated some changes in patent policies, the transfer of technological improvements discovered in university laboratories to the private sector has accelerated. Thus, the number of academic

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investigations supported by the pharmaceutical industry has increased and researchers are encouraged to take part in industry-supported projects. Licit execution facilitates an increase in the collaboration between academia and industry (Angell, 2000; Warner and Gluck, 2003; Rubin, 2005). The ratio of industry-supported articles to total articles in 1981 was 21.6:78.4; however, this ratio doubled to 40.8:59.2 by 1995. If biomedical investigations are taken into account, this increase is 4-fold (Rampton and Stauber, 2002).

Financial support for 89%-98% of comparative drug studies was estimated to come from the pharmaceutical industry, and the results of these studies have been in the favor of the pharmaceutical companies that manufacture the investigated drug (Safer, 2002).

Numerous studies have been conducted to investigate the relationship between financial support and results of clinical studies in different fields of medicine (Davidson, 1986; Djulbegovic et al., 2000; Als-Nielsen et al., 2003). After enactment of the patent law a significant relationship between pharmaceutical industry support and positive study results was detected in a review that compared the results of 117 controlled clinical trials, according sources of financial support (Davidson, 1986). In reviews published in the following years the number of results in favor of supporting drug companies was reported to have increased. In a review, Djulbegovic et al. (2000) compared 136 randomized trials concerning the treatment of multiple myeloma according to sources of financial support and detected a tendency to report more positive results in favor of novel treatment modalities in industry-supported investigations compared to non-industry-supported studies. Als-Nielsen et al. (2003) conducted an investigation that evaluated 167 randomized drug trials and found that more positive results were reported for industry-supported investigations due to interpretation bias.

In response to the increase in the pharmaceutical industry's budget devoted to investigative research and in the number of the investigators taking part in these projects, bias in study results and the concept of "conflict of interest" has developed. There is no common definition of conflict of interest; however, very simply, conflict of interest is defined as a significant influence on the design, execution, and publishing of research due to financial or non-financial benefits afforded investigators (Warner and Gluck, 2003).

If we look at the concept of conflict of interest from a wider point of view, the point determining the solution of the conflict is the characteristic of concept that the conflict arise from, rather than who are involved in the conflict. Thus, conflict of interest differs from competing interests. The "competing interests" concept is the probability that individuals or an institution(s) can affect an investigation inappropriately because of financial, personal, or academic relationships with other people or institution(s), whether causing a bias or not; however, bias in an investigation due to the relationships mentioned above is defined as conflict of interest (Gupta and Choudhury, 2003).

Conflicting interests is a rather larger concept. Apart from conflict of interest, using someone's institutional authority for personal benefit or someone else's and the subsequent absence of objectivity also lead to a conflict of interest (Healy, 2002).

Situations leading to the development of a financial conflict of interest have been defined as follows: i) a clinician or an investigator is a member, stockholder, or board member of a pharmaceutical company, ii) an investigator provides consultation, consistently or inconsistently, to a pharmaceutical company, iii) an investigator is an official spokesperson for a pharmaceutical company, iv) an investigator receives a regular salary or honorary financial support (honorarium) from a pharmaceutical company, v) an investigator is the clinical investigator of the supporting pharmaceutical company, vi) an investigator received financial support from a pharmaceutical company for a study, vii) an investigator is financially indebted to a pharmaceutical company (Fava, 2007).

In recent years the relationship between the pharmaceutical industry and scientific academia has been more conspicuous, not only in psychiatry, but in other fields as well. Numerous conflicts of interest contravening scientific principles have led to suspicions related to information about drugs for treatment or etiologic agents of diseases (Hardell et al., 2007). Thus, in recent years the results of 2 large psychiatry studies conducted in USA and UK (Lieberman et al. 2005, Jones et al. 2006) that did not have pharmaceutical industry support revived the questions about sources of bias in industry-supported investigations. Because both studies revealed that the efficacy, side effects, and effects on the quality of life of second-generation antipsychotics had a similar efficacy compared to a first-generation antipsychotic drug. These results led to suspicion about the reliability of the results of several industry-supported investigations that reported results in favor of second-generation antipsychotics, raising concern about the effects of pharmaceutical

company financial support on the results of the studies (Haddad and Lieberman, 2007).

The present review aimed to evaluate the effect of financial conflict of interest on pharmaceutical company-supported psychiatry investigations.

Material and Methods

In order to evaluate the effect of financial conflict of interest due to pharmaceutical industry-supported psychiatry investigations, the Turkish and international psychiatry literature were searched. PubMed, Medline, ProQuest, EBSCOHost, and PsycINFO databases were searched for English language articles published between 1968 and 2007 with different combinations of the key words, which included conflict of interest, competing interest, and psychiatry. The articles obtained and the references of these articles were examined and those appropriate for this review were discussed accordingly. In order to find articles concerning this issue, the same key words in Turkish were used for a search in Turkish Medline and the Çukurova Index databases.

While 7 investigations examining the relationship between clinical studies in psychiatry and financial conflict of interest were found in the English language literature, there were no studies concerning this subject in the Turkish databases.

RESULTS

The Effect of Financial Conflict of Interest on Psychiatric Investigations

Ahmer et al. (2005) compared the results of 188 randomized controlled trials published between 1998 and 2003 in 4 psychiatry journals (Acta Psychiatrica Scandinavica, American Journal of Psychiatry, Archives of General Psychiatry, and British Journal of Psychiatry), according to financial resources. It was detected that industry-supported investigations reported more positive results than non-supported ones. When the authors examined the factors affecting positive results, they reported that an author(s) being a pharmaceutical company employee was a very strong factor.

Kelly et al. (2006) examined 542 clinical trials that were published between 1992 and 2002 in 4 psychiatry journals (American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, and Journal of Clinical Psychopharmacology) and detected that the rate of industry-supported investigations increased form 25% to 57% during that 10-year period. Furthermore, they reported that the positive result rate was 78% among the investigations supported by the company whose drug was investigated, 48% among the non-supported investigations, and 28% among the investigations supported by a rival drug company.

Perlis et al. (2005) examined all clinical trials published between 2001 and 2003 in 4 psychiatry journals (American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, and Journal of Clinical Psychopharmacology), with respect to financial support and author conflict of interest. They included a total of 397 clinical trials, 167 of which were double blind placebo controlled investigations. They reported that 60% of the trials were supported by the drug industry and that the financial support of the trials did not affect the results. On the contrary, the authors reported that in double blind placebo controlled trials, financial conflict of interest between investigators and pharmaceutical companies whose drugs are studied increases the likelihood of results in favor of the drug 4.9-fold, a statistically significant rate.

Mongomery et al. (2004) compared the results of randomized controlled trials of second-generation antipsychotic drugs, with respect to their financial support. When compared to non-supported studies the results of industry-supported studies were in favor of second-generation antipsychotics significantly more often than first-generation drugs. Furthermore, they reported that the results of the articles in which the lead author was associated with a supporting pharmaceutical company tended to favor second-generation antipsychotic drugs.

Heres et al. (2006) investigated whether or not there was a relationship between the source of financial support and drug efficacy in 42 clinical trials that compared second-generation antipsychotic drugs to each other. They detected that 33 of these studies (78.6%) were supported by the pharmaceutical industry and 90% of the studies reported results in favor of the drugs produced by the companies in support of the studies. When they examined the studies that compared 2 matched antipsychotic couple with each other, the results might be in contrast with each other according to whether the supporting company is manufacturer or rival company.

The effect of financial support on study results was also shown in meta-analyses that evaluated clinical studies. Moncrieff (2003) included 10 investigations that compared the efficacy of clozapine to typical antipsychotic drugs in a meta-regression analysis, and found a relationship between reports of the superiority of cloza-

pine over typical drugs and financial support provided by the company that produces clozapine. Freemantle et al. (2000) investigated the effect of the pharmacological mechanism of different antidepressants to study results in a meta-regression analysis, and reported that financial resources had an important effect on study results, though not statistically significant.

The Factors Influencing the Results of Industry-Supported Clinical Studies

The negative effect of conflict of interest on the execution and publishing of investigations has been known for years (Montaner et al., 2000; Warner and Gluck, 2003). In industry-supported studies there are some interventions at different stages of the studies (such as in planning, analysis of data, and publishing or not publishing the results) initiated to obtain results in favor of supporting companies' products (Çekin and Yazıcı, 2000; Montaner et al., 2000; Safer, 2002). For this reason, which particular facets of conflict of interest influence studies in different stages of an investigation is an important issue.

Study Planning Stage

Multi-center industry-supported clinical studies are mostly planned by pharmaceutical companies (Council on Scientific Affairs 1990); as such, they may have influence on the results, even before a study begins. In clinical studies one of the factors influencing study results is poorly defined inclusion criteria for participants (Safer, 2002; Heres et al., 2006). For example, treatment-resistant schizophrenia is a controversial concept (Miller et al., 2004). In industry-supported studies that compared second-generation antipsychotics to each other and to haloperidol in schizophrenia patients resistant to treatment, it was indicated that most of the second-generation antipsychotics, except clozapine, were significantly related to positive results in terms of efficacy, drug coherence, side effects, and quality of life. During a 6-8 week period 35%-65% of the patients were reported to have responded well to treatment in these studies; however, due to an imprecise definition, it is uncertain that all of the patients were really treatment-resistant schizophrenics. For example, Bondolfi et al. (1998) included patients that were intolerant to treatment as well as those that were resistant to treatment in their study. Furthermore, the designs of these studies may have produced a bias in favor of new drugs because the patients included generally responded inadequately to first-generation antipsychotic drugs, but were subsequently randomly assigned to either a new drug or another first-generation antipsychotic drug (Marder, 1999).

Dose adjustment and dose increasing periods are quite important issues influencing the results of pharmaceutical industry-supported studies (Freemantle et al. 2000). A remarkable example of this bias is the comparison of second-generation antipsychotics with high-dose haloperidol. In most of the industry-supported studies, pharmaceutical companies compared their second-generation antipsychotic drug with at least a 20-mg daily dose of haloperidol (Lapierre et al., 1990; Patris et al., 1990; Chouinard et al., 1993; Simpson and Lindenmeyer, 1997); thus, the impression that fewer extrapyramidal side effects are associated with second-generation antipsychotics, compared to haloperidol, was given. A similar example can be observed in studies that compared second-generation antipsychotic drugs to each other. In these studies more side effects due to risperidone were reported than the drug in comparison by administering high doses of risperidone (Marder, 1999; Purdon et al., 2000; Sechter et al., 2002).

The dose increasing period is also an important factor that influences the results pharmaceutical industry-supported studies. Rapidly or slowly increasing the dose of the drug in comparison (titration period) may create the impression that the drug produced by the company financing the study is more effective or causes fewer side effects (Safer 2002, Heres et al. 2006).

Data Analysis Stage

Pharmaceutical companies have strict control and decisiveness on data collection, data quality control, data analysis, and data interpretation; therefore, evaluation of raw data by investigators other than those associated with pharmaceutical companies is almost impossible. This condition restricts secondary analysis, which is necessary for future studies, and biases the interpretation of results (Montaner et al. 2001). The analysis of data by pharmaceutical companies is an important factor influencing the results of the studies they fund. Kessler (1992) indicated that positive results obtained in drug comparison studies supported by the pharmaceutical industry might be related to an end point that was not accounted for in the primary hypothesis of the study. At the point that the drug produced by the company supporting the study is determined to be superior to the comparison drug, study termination would influence the results in favor of the pharmaceutical company.

Publishing or Not Publishing the Results

Sharing the results of scientific research is necessary for the advancement of science; however, in pharmaceutical industry-supported investigations, contracts signed between the company and investigators restricts sharing of the results (Rennie, 1997).

For instance, in a study by Blumenthal et al. (1997) it was detected that among 2167 investigators, 19.8% had delayed publication of completed study results for more than 6 months in order to gain time for patent application, to prevent negative financial effects of the results, and to block sharing unwanted results.

Another factor that gives rise to a bias in industry-supported study results is known as "salami science". This was first described by Huth (1986) and refers to publishing multiple reports based on just 1 study. Among industry-supported investigations in psychiatry, multiple publishing of studies was detected (Flanagin et al., 1998; Melander et al., 2003). Regarding this issue, Huston and Moher (1996) evaluated studies of risperidone and detected 20 articles and citations, as well as several randomized double blind controlled study articles that were not published yet; however, they figured out that all of these publications and citations belonged to only 2 multi-center and 7 smaller studies.

Despite making important contributions to an investigation and/or writing an article, an investigator not present among the authors of an article is known as a ghostwriter. In some pharmaceutical industry-supported studies the names of the investigators that provided important contributions to the design and execution of a study are not listed among the authors of the study. This is done to mask pharmaceutical company support for studies and minimize any negative interpretations that may result from the public disclosure of their support (Safer, 2002).

Flanagin et al. (1998) investigated ghost authorship by sending questionnaires to the authors of 809 studies randomly selected from the journals with high impact factor (Annals of Internal Medicine, Journal of American Medical Association, New England Journal of Medicine, American Journal of Cardiology, American Journal of Medicine, and American Journal of Obstetrics and Gynecology) and reported that the rate of ghost authorship was 11%. Mowatt et al. (2002) reported that the rate of ghost authorship was 9% based on the replies from 362 lead authors of 577 articles in the Cochrane Database in 1999; however, they suggest that this rate might be higher, as only 68% of their questionnaires were returned.

Gøtszche et al. (2007) investigated ghost authorship in randomized pharmaceutical industry-supported studies. When they compared the names of the authors in industry-supported articles approved by the Copenhagen and Fredericksburg Local Ethics Committees and the names in the protocols of the studies presented to the ethics committees, they detected a rate of ghost authorship of 73%. This rate increased to 91% when the names of investigators listed in study acknowledgements were included in the ghost authorship context despite meeting authorship criteria.

Discussion and Conclusion

Financial conflict of interest in psychiatry investigations supported by the pharmaceutical industry leads to a bias in the results that favor the drugs produced by the companies supporting the research (Freemantle et al., 2000; Moncrieff, 2003; Montgomery et al., 2004; Ahmer et al., 2005; Perlis et al., 2005; Heres et al., 2006; Kelly et al., 2006). These results are similar to findings of previous reviews that evaluated the bias in results of pharmaceutical industry-supported studies in other fields of medicine (Davidson 1986, Djulbegovic 2000, Safer 2002, Als-Nielsen 2003). Biased study results arise from interventions in the planning, data analysis, or publishing phases by the supporting company and/or the investigator(s) (Safer 2002, Heres et al. 2006).

The effect of financial conflict of interest on research results casts suspicion on the reliability of research in psychiatry and other fields of medicine, as well as on the reputation of the journals that publish these reports (Fava, 2007; Nierenberg, 2007; Tohen, 2007); therefore, some precautions are needed in order to decrease the effects of conflict of interest. These precautions include: disclosure of the relationships between authors and the pharmaceutical industry at academic conferences and in academic journals; the development of advisory committees by academic institutions to specifically address conflict of interest; to produce common policies concerning conflict of interest by pharmaceutical companies and academic journals (Fava, 2007).

Explaining the Conflict of Interest

The rate of the conflict of interest in scientific research is quite high. In a study that evaluated the conflict of interest of 170 panel members on the advisory committees of DSM-IV (APA 1994) and DSM-IV-TR, 95

(56%) were found to have a conflict of interest with at least 1 drug company. This rate increased to 100% when conflict of interest of the members attending sessions on diagnostic category generation, in which pharmacotherapy is prominent, were included (Cosgrove et al. 2006).

Nonetheless, the high rate of conflict of interest in the academic literature does not necessarily mean that the authors explain their relations with pharmaceutical industry. For example, Krimsy et al. (1996) evaluated the frequency of drug industry-related conflict of interest among 1105 investigators whose investigations were published in different journals in 1992. They reported that 1/3 of the authors had a financial conflict of interest with the pharmaceutical industry, but almost none explained this relationship. In another study Choundry et al. (2002) evaluated 44 clinical practice guideline authors, including clinical practice guidelines for depression, in terms of conflict of interest. They found that 87% of the authors had a conflict of interest with the pharmaceutical industry; however, such conflict of interest was indicated only in 2 of the clinical practice guidelines.

Advisory Committee for Conflict of Interest

It was indicated that the establishment of an advisory committee on conflict of interest could decrease its negative effect on academia, investigators, and on those of volunteer research participants (Rubin, 2005). It was emphasized that these committees should not have a relationship with any pharmaceutical company. Such independent committees could contribute to reducing the negativity that results from conflict of interest (Fava, 2007); however, Nirenberg (2007) indicated that this kind of independent committee could lead to a negative bias for the pharmaceutical industry.

Constitution of a Policy for Conflict of Interest

There is no common point of view concerning the determination of the limits of conflict of interest and the identification of related policies. While some institutions define any kind of relationship with a pharmaceutical company as a conflict of interest, others define this concept as a gain of $10,000 to $20,000 from a pharmaceutical company in addition to an investigator's total yearly income (Rubin, 2005). The discrepancies between institutions concerning conflict of interest prevent a common policy from being established. For example, Harvard Faculty of Medicine restricted academicians from buying more than $20,000 worth of stock in research-supporting companies; however, the faculty directors were forced to abolish this restriction because their best academicians started to leave the university (Angell, 2000). In recent years, some common guidelines have started to be published in USA due to these emerging problems in order to prevent the negative effects of conflict of interest. In the guideline published by the Association of American Medical Colleges, it was indicated that investigators should not participate in studies support by companies from which they earn $10,000 per year in addition to their regular income (AAMC Task Force of Financial Conflicts of Interest in Clinical Research, 2003). Moreover, 2 other guidelines were developed in 2002 and 2004 by the US pharmaceutical industry concerning conflict of interest. In these guidelines the execution of research and the relationships between pharmaceutical companies and clinicians were discussed (Rubin, 2005).

Biased results of pharmaceutical industry-supported investigations damages the reputation of publishing journals. For this reason, numerous academic medical journals took serious actions concerning pharmaceutical industry-supported studies. For instance, the Journal of the American Medical Association (JAMA) instituted a rule that before publishing industry-supported studies, the reliability of the data should be approved by an author of the study who is not an employee of the pharmaceutical industry, and that the data should also be analyzed by an independent statistician (Fontanarosa et al., 2005).

In 2001, 13 editors, including the editors of journals with a high impact factor, such as the New England Journal of Medicine, JAMA, The Lancet, and Annals of Internal Medicine, published a common announcement. In this announcement these editors indicated that clinical research should be used carefully and its use primarily for marketing was an abuse of an important tool; therefore, they pointed out, the relationship between authors and pharmaceutical companies, and the role of supporters of the investigation should be explained in detail. Also, a declaration would be signed with the authors of the study concerning they controlled publishing decision, reached the data and accepted the reliability of the investigation (Davidoff et al., 2001).

Addition to general medicine, conflict of interest causes research results in the filed of psychiatry to favor supporting pharmaceutical companies. Biased results arise from interventions during the planning, data analysis, and publishing (or not publishing) phases of an investigation.

Regarding the increase in the rate of pharmaceutical

industry-supported studies during the last decade, one could consider that these problems detected in the international literature also occur in Turkey; however, there are no investigations of the effect of financial conflict of interest on research results in Turkey. Nonetheless, important progress has been made concerning scientific research and publishing ethics in Turkey. For example, a questionnaire sent to editors of the journals included in TÜBİTAK Turkish Medical Literature can be considered an important step regarding this issue in Turkey.

According to the results of this study, several problems were identified: Journals were supported mostly by the pharmaceutical industry via advertisements; imprecise guidlines for the function of publishing committees and editors; imprecise evaluation instructions for consultants to follow (Aksit and Arda, 2003). For the correction of such problems in Turkey, a symposium has been arranged annually since 2003, The National Periodical Publishing Symposium on Medical Sciences, organized by TÜBİTAK-ULAKBİM (Turkish National Academic Network and Information Center). Despite developments in the field of scientific research and publishing ethics, the lack of an investigation evaluating the effect of financial conflict of interest on research results in Turkey is a serious deficiency. Thus, preventing the negative effects of conflict of interest is an important issue for researchers, the pharmaceutical industry, academic institutions, and Turkish scientific journals.

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