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PAXIL, WELLBUTRIN AND AVANDIA- A PERFECT COCKTAIL OF MEDICO MARKETING MALPRACTICE

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ABSTRACT

Pharmaceutical industries play the central role in patient care through the process of drug discovery. The noble deed of discovering magic bullets to heal mankind is often neutralized by unethical medico-marketing strategies employed by the pharmaceutical industries. Disreputable acts such as misbranding, selective reporting, data dredging, misusing continuing medical education programs to provide tailored information lead to largest healthcare fraud settlement of US$3billion in the United States by GlaxoSmithkline LLC (GSK). This article analyses the indifferent medico-marketing practices of the pharma major for their products Paxil, Wellbutrin and Avandia. Candid efforts from the regulatory bodies, pharmaceutical industries and practicing doctors are the need of the hour to combat the menace of withholding safety data, illegal marketing which eventually results in poorer patient outcomes.

Keywords: Paxil, Wellbutrin, Avandia, medico-marketing, Malpractice

INTRODUCTION

There has been an increasing trend of overt physician-pharmaceutical industries interactions that often results in huge revenues for the manufactures and poor outcomes in patients. Various studies investigated the nexus between physician and pharmaceutical industries and the attitude of physicians towards the largesse from the pharmaceutical industry. [1-6] It is increasingly evident that the benefits received from the pharmaceutical industries often influence the prescribing behavior of the clinicians. We are witnessing an era in which physicians are continuously pressurized by the sales force of pharmaceutical companies and the interests of the patients are always considered as a last priority. The cajoling of medico marketing personnel coupled with captivating gifts, sponsorship of foreign trips and arrangements of social meetings at exotic locations makes the prescriber more vulnerable to the directives of pharmaceutical companies. [7-11]

The current situation in which the doctors are entitled to use the prescription drugs for their off-label use complicates the issue further. Pharmaceutical industries take advantage of this situation to promote their drugs for their unapproved/off-label uses. These marketing misbehaviors may sometimes accompanied by the breach of regulatory requirements set by drug control bodies like FDA. This article will objectively explains the case of Paxil, Wellbutrin and Avandia through which the readers can get a glimpse of aggressive unethical marketing and non-disclosure of post marketing studies to FDA implemented by the pharma major GLAXOSMITHCLINE LLC (GSK). At the outset the author wish to state his respect for GSK and its commitment to community and healthcare including its recent dope testing activity in London Olympics 2012 to make it the most fair Olympics conducted ever. Nevertheless it is important to scientifically document the disappointing conduct of GSK with afore mentioned drugs. The charge sheet of US attorney general to GSK and the GSK plea agreement are the primary sources for the write up of this article. [12, 13]. Any differences of opinion about this review can be forwarded to author.

THE LUCRATIVE COCKTAIL OF MEDICO MARKETING DECEPTION:

The value of global pharmaceutical market has been projected to reach US$1.1 trillion by 2014, according

to IMS Health Market Prognoses. [14] It is an open secret that pharma majors leave no stones unturned to cash in this recession-free scenario. In pursuit of huge revenues, the ethical boundaries of marketing are often breached. Recently the court settlement of US$ 3 billion by the pharma major GSK raised some crucial queries on the consciences involved in marketing drugs. The issue of Paxil, Wellbutrin and Avandia clearly indicate the fissure of moral standards that exist in the pharmaceutical industry and it is imperative to document factually.

The Issue of Paxil: Paroxetine hydrochloride, a selective serotonin reuptake inhibitor is manufactured and marketed by GSK as Paxil. FDA approved paxil in the year 1992 for the treatment of depression in adults. The unacceptable practices related with paxil can be detailed under two main divisions such as Selective reporting coupled with data dredging and misbranding. The manufacturers of paxil have conducted three placebo controlled clinical studies (Study 329,377 and 701) in children and adolescents to test its safety and efficacy against depression. All these studies were conducted from 1994 to 2001.

Study 329 compared the clinical efficacy of paxil and a standard drug imipramine with placebo. It was found that paxil did not do better on two primary end points and more importantly 11 SAE (serious adverse effects) which include agitated suicidal behavior were found. The placebo group was found to be safer than paxil in terms of SAEs. It was revealed that GSK contracted a scientific services company to develop an article based on study 329. Just for the publication sake and for the possible business interest of their client, the scientific services company involved in data dredging. Their document stated that paxil showed superiority over placebo on 4 out of 8 newly inserted endpoints which were not specified in the original protocol.

The paper was initially sent to JAMA (Journal of American Medical Association) and it was rejected and later on the same article was sent to less demanding journal JAACAP (Journal of the American Academy of Child and Adolescent Psychiatry). It is worth mentioning here that the article had 22 authors out of which only 2 were GSK employees. The JAACAP article's abstract and conclusion stated that paxil was clinically effective and safer to use in the treatment of depression. The JAACAP article was later retracted by the editorial team and hence it is not referenced in this article.

Further it was observed that there was a striking/bothersome difference between the initial draft and the printed version of the controversial article. The initial version stated that11 patients on paxil experienced SAEs which may be related to paxil treatment. Later on it was modified in the printed version that out of 11 patients who experienced SAEs, only headache (experienced by 1 patient) was considered to be related to paxil. Paxil sales force received a copy of the JAACAP article and many representatives were supposedly used the information presented in the journal to promote paxil's usage in adolescents. Studies 377 and 701 failed to show any superiority of paxil over placebo in terms of primary and secondary endpoints. The results of these studies clearly highlighted the failure of paxil in demonstrating superiority over placebo.

In a nutshell, the results of Study 329, 377 and 701 were discouraging. The manufactures neither published the results of studies 377 and 701 nor disclosed the results to their paxil sales team. The misleading information from the study 329 was published and circulated among the prescribers through paxil sales team. The misbranding aspect of paxil can be considered as a striking example for modern day marketing (mal) practices employed by various pharmaceutical majors.

According to FDCA, the manufacturers are not supposed to market and promote a drug for its off-label/unapproved use but the doctors are allowed to prescribe the drugs for their unapproved use based on their medical judgment. Many pharmaceutical companies take advantage of the doctor's freedom to prescribe medicines for their off- label use and try to influence the prescribing behavior. Doctors are hence highly susceptible to the pressures of the pharmaceutical sales force and prescribe medicines for their unapproved use.

GSK spent lavishly on conducting forums, social events to promote off-label uses of paxil. It has conducted eight forums on paxil and tried to influence doctors to prescribe paxil for the treatment of depression in adolescents. A lecture was given at all the forums conducted at exotic locations. These lectures contained only favorable results from study 329. The unfavorable findings of study 329 were not presented. Needless to say that there was no mentioning about the studies 377 and 701 in these forum lectures. Thus GSK used paxil forums for the dissemination of selective and misleading information about paxil's efficacy in adolescents with depression. Various lunches, dinner and spa programs were sponsored by GSK to promote paxil's use in adolescent depression. Further free samples

were given to doctors to use in children and adolescents.

The Issue of Wellbutrin: Bupropion hydrochloride was marketed by GSK as wellbutrin. Bupropion Hydrochloride is an amino-ketone antidepressant which is mainly indicated for Major Depressive Disorder (MDD). The ambiguity on the mechanism of action of wellbutrin has not yet been resolved as it has no effect on both norepinephrine and 5-hydroxy tryptamine-2 (5-HT_2) receptors [15]. GSK promoted wellbutrin with an array of inappropriate claims that it can be used for sexual dysfunction, obesity, various forms of addictions such as drug, alcohol and gambling, to counteract side effects of other antidepressant medications. Some representatives referred wellbutrin with an attractive phrase 'happy-horny-skinny pill' and portrayed the drug as miracle molecule that influences the quality of life.

As with paxil case, off-label informations about wellbutrin were disseminated to the doctors attending lavish meetings at exotic locations like Jamaica and Bermuda. Needless to say all these meetings are sponsored by GSK with the hidden agenda to instigate doctors to prescribe wellbutrin for its unapproved use. These meetings were often labeled as 'advisory board meetings' or 'consultant meetings' to create a pretense that it was trying to gather some usable information from the practitioners.

Further GSK sponsored many CME (Continuing Medical Education Program) programs for the doctors to deliver off-label informations of wellbutrin. Some of these CME programs were conducted as exactly as choreographed by GSK and informations that caters the interests of the pharma major were disseminated in these meetings.

The Issue of Avandia:
GSK developed a prescription drug Avandia (rosiglitazone maleate) an anti-diabetic medication, which acts as an insulin sensitizer. The new drug application of Avandia was approved by FDA in May 1999.

In the year 2001, GSK initiated two studies namely Study 211 and RECORD. These two studies were initiated at the request of European regulatory authorities to reevaluate the cardiovascular safety of the drug.

GSK in its protocol stated that the Study 211 was initiated to investigate anti-diabetic therapy on cardiac structure and function plus cardiovascular morbidity and mortality in Type-2 diabetic patients with preexisting congestive heart failure.

RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes trial) was initiated by GSK to investigate long-term cardiovascular effects in two groups of patients such as those who were receiving popular sulfonylurea+ Metformin (SU+MET) and those who were receiving rosiglitazone along with their primary medications such as metformin or sulfonylurea.

Apart from the afore mentioned studies, GSK conducted two more studies such as APPROACH (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History) and ADOPT (A Diabetes Outcome Progression Trial) which were initiated to address the cardiovascular safety issues and clinical efficiency respectively. In its periodic report to FDA, GSK did not disclose the initiation of study 211 and RECORD. To make the issues shoddier, the status report of certain post marketing studies such as Study 211, RECORD, APPROACH and ADOPT were not disclosed to FDA by GSK on time. This was clear breach of GSK's commitment to FDA on the timely disclosure of information regarding the initiation, execution and results of post marketing studies.

CONCLUSION AND RECOMMENDATIONS:

Misbranding, selective reporting, data dredging, influencing therapeutic judgment, swaying CME programs of doctors and non-disclosure of periodic reports were the active ingredients of the medico-marketing malpractice implemented by the pharma major GSK to promote its drugs paxil, wellbutrin and avandia. To fill the coffers, the patients' interests went off-track and GSK was spared with just a penalty of US$ 3 billion. The New York Times newspaper, referring to IMS Health, a data group that consults for drug makers revealed that Avandia, racked up $10.4 billion, Paxil gave $11.6 billion and Wellbutrin provided $5.9 billion during the years covered by the settlement [16]. Despite the quantum of offence, GSK was spared with little money (when compared with its earnings) and certain administrative resolutions. It is important to note that no individual was punished or at least reprimanded. A three pronged approach can impede the process of medico marketing malpractices. First and foremost, the FDA and other regulating bodies should device a mechanism of direct monitoring of the studies conducted instead of totally relaying on the reports

submitted by the companies. Secondly, the companies should provide incentives for the sales representatives based on the quality of information disseminated rather than the size of sales. Lastly the practitioners should put their clients' interest before monitory benefits they receive from the pharmaceutical companies. Thus an inclusive role of three main stakeholders (Regulatory body, Pharmaceutical Companies and Clinicians) is needed to end the menace of proliferation medico-marketing malpractices.

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CONFLICT OF INTEREST: None

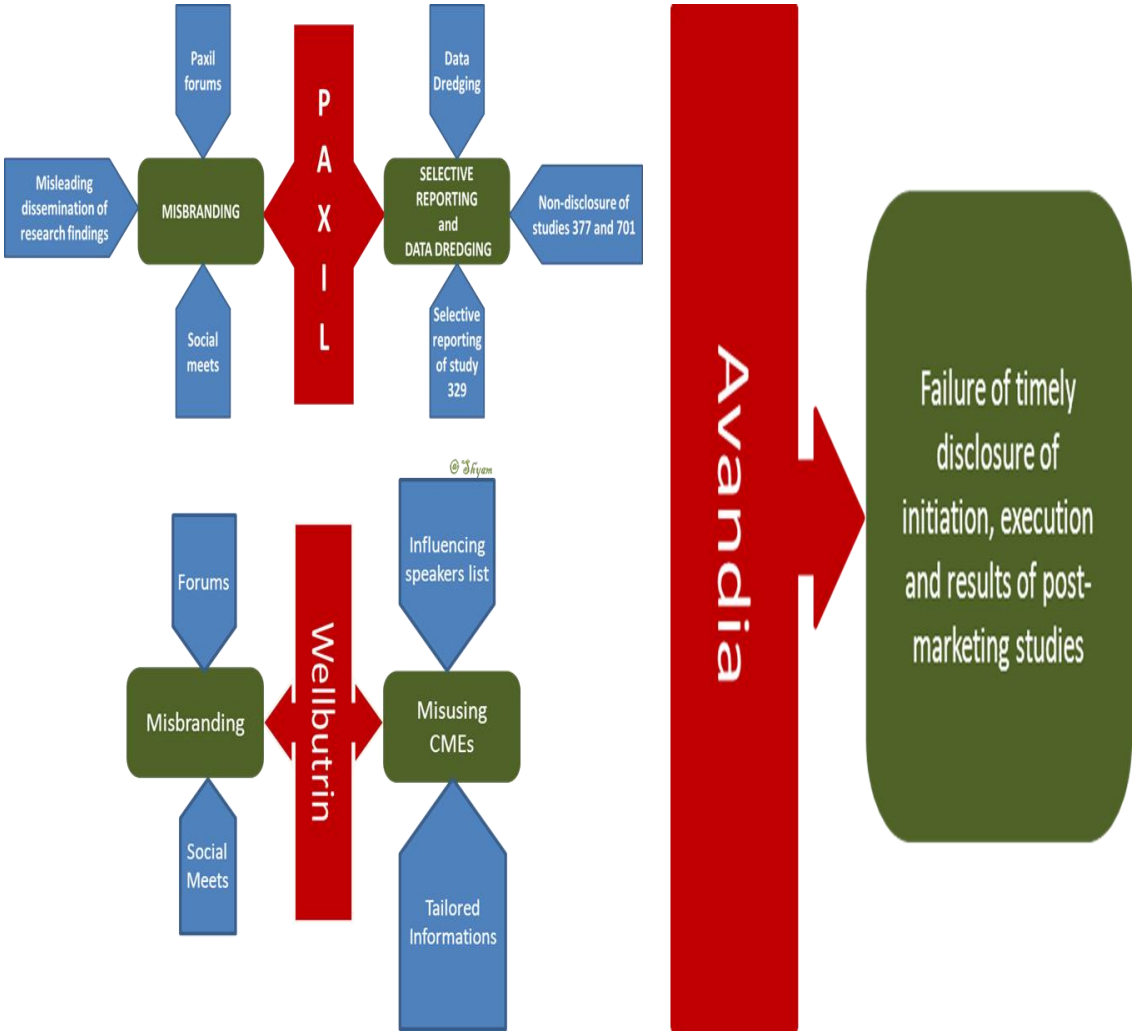

Figure 1: SUMMARY OF THE LUCRATIVE COCKTAIL OF DECEPTION INVOLVING PAXIL, WELLBUTRIN AND AVANDIA

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