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ORIGINAL REPORT

Psychosocial Modifiers of Drug Prescription: The Hidden Face of Pharmacology?

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SUMMARY

Apart from placebo, there is scant medical knowledge regarding the influence of psychosocial effect modifiers in pharmacology. Phenomena such as the nocebo, Hawthorne, Oedipus and complacency effects have been previously described as sources of bias in clinical trials; however, the effects related to prescription patterns have been widely ignored to date. Under certain circumstances, psychosocial effects may even be catalysts for changes in the official regulations on drug prescription — changes often lacking an adequate scientific basis — and, subsequently, induce major changes in drug use worldwide. In spite of this, the study of psychosocial effects in pharmacology has been confined to anecdotal reports. The present overview of this topic is aimed at encouraging the identification of psychosocial effects in pharmacology. It also suggests that commercial case studies of drugs are a suitable method for studying prescription and effect modifiers. Triazolam's commercial history provides a good example of this approach. A better knowledge of these effects may contribute to a better understanding of the prescription habits observed in clinical practice. It may also prevent paradoxical changes in prescription patterns or in drug regulations. © 1998 John Wiley & Sons, Ltd.

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INTRODUCTION

In most cases, current knowledge regarding psychosocial effect modifiers of drug response is limited to the placebo effect.[1–3] However, there are other effect modifiers that have been described in the literature, such as: the nocebo effect,[4] the Oedipus effect,[5] the complacency effect,[6] the Lourdes effect[7] and the Hawthorne effect.[8] The differences and the relevance of such effects in pharmacology has been discussed elsewhere.[7] A number of designs may eliminate the influence of these factors in clinical trials,[9] but they will still play a relevant role in clinical practice. Therefore, the study of these effects is particularly relevant to pharmacoepidemiology. Unfortunately, we lack an operational definition and classification of these and other psychosocial effect modifiers. A tentative description of these effects is provided in the first section of Table 1.

Some of these effects may not only alter drug response, but also drug prescription habits. Nevertheless, the effect modifiers which influence drug prescription have been described only rarely in the scientific literature. Probably the better known are the tomato effect and the mass-media effect. The tomato effect describes the rejection of an effective drug on the grounds of non-scientific beliefs. It is based on the fact that tomatoes were widely thought to be poisonous in America, until an early nineteenth-century physician dared to eat tomatoes as a public demonstration of their safety.[10] This effect has been used to describe the fate of

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Table 1 — Psychosocial effect modifiers in pharmacology

A. Effect modifiers of therapeutical response
1. Placebo effect (in pharmacology) The administration of an inert substance determines significant clinical effects, which in a variable proportion of subjects, and in certain pathologies, can be compared to those of an active compound of reference. In a double-blind clinical study, it is considered that this effect depends neither on motivation nor expectancy.
2. Nocebo effect (in pharmacology) The administration of an inert substance determines significant adverse effects, which in a variable proportion of subjects, and in certain pathologies, can be compared to those of an active compound of reference. In a double-blind clinical study, it is considered that this effect depends neither on motivation nor expectancy.
3. Hawthorne effect (in pharmacology) A strong incentive motivation in the subjects of a study or its research personnel conditions the study's final results. Incentive motivation is characterized by the presence of objective or material benefits.
4. Oedipus effect Under certain circumstances, if the physician has strong expectations regarding the drug, this will condition the final response: 'a self-fulfilling prophecy'. Expectancy differs from incentive motivation in that there are no objective or material benefits.
5. Lourdes effect Under certain circumstances, if the patient has strong expectations regarding the drug, this will condition the final response.
6. Complacency effect The desire to present positive results on the part of the researchers conditions an abnormally high rate of such results.
B. Effect modifiers of prescription habits
1. Mass-media effect Under certain circumstances, a news story in the mass media carries more weight than current scientific knowledge on a subject, even among professionals.
2. Ostrich effect Under certain circumstances, precise and detailed knowledge of a drug's side-effects and partial contraindications can lead the physician to choose an alternative product about which scientific information is insufficient or scarce.
3. Preacher effect Under certain circumstances, an expert's beliefs carry more weight than scientific evidence in determining prescription patterns and administrative policy-making.
4. Scapegoat effect When a family of drugs suffers from stigmatization, one product only can be the focus of criticism and taken off the market, even though it does not differ substantially from others in the same group.
5. Tomato effect Under certain circumstances, a drug empirically demonstrated to be efficacious can be rejected on the grounds of non-scientific beliefs and/or lack of knowledge about its precise mechanism of action.

electroconvulsive therapy in schizophrenia.[11] Other effects of this kind are the scapegoat effect, the preacher effect and the ostrich effect. A brief description of these prescription modifiers is provided in the second section of Table 1.

Psychosocial effects related to prescription habits can be identified via naturalistic studies or long-term analyses of prescription patterns at local, national and international levels. It is important to note that these habits may deviate significantly from official recommendations and good practice guidelines, or the prescription patterns in academic or institutional settings. Unfortunately, naturalistic and linked health data-base studies have not focused on these issues. On the other hand, commercial case studies of drugs provide a fair amount of information, which has been largely overlooked, and which enables us to identify attitudes and behaviour patterns of the general population and health personnel. These commercial case studies

thus cease to be merely anecdotal, becoming a useful research tool for studying psychosocial effect modifiers.

Psychopharmacology provides several examples of the influence of these phenomena on physicians' prescription habits. The triazolam (Halcion®) case is one of the best documented examples.[7,12] Psychosocial effect modifiers also play an important role in the commercial histories of fluoxetine (Prozac®),[7,13] and the antipsychotic clozapine (Clozaril®).[14] Data from the United States and Europe are considered here. References to television programmes, newspaper articles or best-sellers are not included in the References.

COMMERCIAL HISTORY OF TRIAZOLAM (HALCION®)

Triazolam is a short half-life benzodiazepine which was marketed during the 1970s. Its side-effects are similar to other short half-life hypnotics from the same family.[15] Until 1989, triazolam was the most prescribed hypnotic in many countries. In spite of this, several non-scientific factors, including a media campaign against the drug, provoked a sharp drop in the prescription of triazolam in several European countries, where it is now a marginal product. Rothschild[12] has reviewed this odd case, which is summarized here.

In 1979, a Dutch journal published an article entitled 'Halcion: A harmless hypnotic?' which described four patients who had experienced adverse reactions to triazolam. The media campaign was strongly negative to the drug. One of the press articles was entitled 'Halcion: Worse than the Softenon [thalidomide] Affair'. In August 1979, the hypnotic was withdrawn from the Dutch market for 6 months, and several letters appeared in *The Lancet* both for and against triazolam and its supposed harmful effects.[16,17] The Dutch Registration College decided that it could be reinstated only after several unusual adverse effects were listed on the labelling. The Upjohn Company filed an appeal with the Dutch Council of State, arguing that these requirements went against scientific evidence. In 1985, on the recommendation of the Dutch Council of State, the Crown held that the Dutch Registration College 'had acted hastily and without adequate review of the available data'.[12] Nevertheless, the Dutch case provoked further reactions in other European countries. In 1987, the Spanish Ministry of Health published the following statement in a *Pharmacological Guide for Primary Care*:[18] 'The use of triazolam for the treatment of insomnia is dangerous: a great number of cases of amnesia, frequently accompanied by criminal behaviour, have been described in people taking this drug. Sometimes these cases have led to bewilderment among the patients themselves, their families, judges and police, and it is possible that the role of triazolam in abnormal behaviour has gone unnoticed'.

On 17 February 1989, the scandal broke out again, this time in the United States. The ABC news programme '20/20' aired a segment entitled 'When Sleep Becomes a Nightmare'. The report focused on Ms I. Grundberg, who allegedly murdered her mother while taking triazolam. The media immediately set up a causal relationship between triazolam intake and criminal behaviour, without taking into account the anecdotal nature of this report, any scientific evidence about the issue, or the simple fact that 11 million prescriptions of Halcion® were filled in the United States during that same year.[19] After this incident, the total number of US prescriptions for outpatients fell nearly 23%, to 8.5 million in 1989.[20] In August 1991, *Newsweek* published an article about a document released by Upjohn during the trial, protocol 321, that reported psychiatric problems among jailed convicts in a phase I trial. Apart from the legal aspects, this unpublished manufacturers' research unfavourable to the drug showed methodological problems that were overlooked by those who considered it as major evidence to show that triazolam is a dangerous drug.[21]

In the UK, a sharp decrease in the sale of triazolam was observed in 1989,[22] and triazolam sales stagnated in other European countries. During 1991 a new campaign spread all over Europe. This time, it was accompanied by scientific evidence on the high rate of rebound phenomena, apart from the previously mentioned 'idiosyncratic'' adverse effects of triazolam, such as psychotic symptoms and abnormal antisocial behaviour. After reviewing the scientific literature about this issue, Rothschild[12] concluded: '... the vast majority of papers which have suggested that short half-life benzodiazepine hypnotics could produce idiosyncratic side effects have been authored by a small group of clinical investigators, many of whom worked and/or trained together at the same site and are co-authors on one another's publications'.

The fact that a restricted and related number of authors attracted a large number of citations may

have been influenced by the Matthew effect.[23] This effect is named for a biblical verse, in Matthew 25:29, which says: 'For unto every one that hath shall be given, and he shall have abundance; but from him that hath not shall be taken away even that which he hath'. A detailed comment on these publications[24,25] exceeds the scope of this paper, and they have been reviewed elsewhere.[26] Nevertheless, it is important to note that this group analysed data from a small number of severe insomniacs, some of them with prior psychiatric diagnosis, who were evaluated at a sleep research centre. The extrapolation of findings from specialized settings to the general population may produce a bias which has been documented previously (e.g. the mistaken relationship between febrile convulsions and childhood epilepsy,[27] or the belief that the Dexametasone Suppression Test could be useful as a general diagnostic test for major depression[28]).

Triazolam was suspended by the UK regulatory authorities on 2 October 1991. That same month, the BBC aired a programme entitled 'The Halcion Nightmare', and during a news broadcast in Spain a TV anchorman stated, 'this pill kills', while holding up a Halcion blister.

Shortly afterwards, Halcion® was suspended in Norway and restricted in other European countries in the midst of a fierce campaign against the product, and controversies between the European Union and national agencies. On 9 January 1992, Spain's drug regulatory authority suspended the licence for 0.25 mg tablets of triazolam. The 0.125 mg tablet remained on the market, but the quantity was reduced to 10 per pack. In 9 months the defined daily doses declined by 85%,[29] and total triazolam sales in Spain plummeted from $7.7 million in 1991 to $0.8 million in 1992 and $0.7 million in 1993, remaining stable ever since (data from Upjohn Farmoquímica, Spain).

The FDA CNS Advisory Committee carried out a review of the drug in 1989 and again in 1992, stating that it was a safe and effective hypnotic when used properly. In spite of this, the negative media campaign continued, as did the decrease in prescriptions over the following years. In Europe, some of the restrictions were revoked in 1993, and on 27 May 1994, the Upjohn company won a suit in the UK against the BBC and the psychiatrist who had accused Upjohn of withholding data from research protocol 321.[21] Nevertheless, the war declared by the mass media against triazolam, as well as official regulations, have banished triazolam from many countries. This phenomenon led Walsh and Engelhart[19] to conclude that in certain situations 'the media influence medical practice more than available scientific data'. Indeed, the Halcion® case may be considered a classic example of the media's influence on drug prescription.[19,30,31]

It also illustrates how the preacher effect may influence the regulatory decision process. Under some circumstances it is extremely difficult to adequately ponder all the available scientific data; this is when attitudes and beliefs may influence conclusions more than scientific evidence, even for an experienced evaluator. Then the 'pontificating writings of specialists' — as Dement[32] puts it — may determine physicians' prescription habits and influence the decisions of health authorities, including health regulations. The preacher effect on triazolam shows a strikingly similar sequence of events in different countries, including the scientific data used against the drug (e.g. the Netherlands in 1979; the UK in 1991; Spain in 1992). In fact, the removal of Halcion from the UK market in 1991 reopened the question of whether a court has to examine the correctness of regulatory authorities' decisions. This issue is currently being analysed by the European Court of Justice (Case C-120/97).

TRIAZOLAM AND THE SOCIAL STIGMA OF BENZODIAZEPINES

The fate of triazolam illustrates two other psychosocial modifiers of drug prescription: the scapegoat effect and the ostrich effect.

The history of Halcion® is hard to understand without taking into account the stigma suffered by the entire family of benzodiazepines. The press campaign against benzodiazepines originated a few years after chlordiazepoxide was launched in 1960. During the following years, knowledge about the biological basis of benzodiazepine's action progressed more than that of any other psychotropic drug. Surprisingly enough, better knowledge about these side-effects and their biological bases led to the use in critical cases of alternative drugs that had not been sufficiently studied. Chlormetiazole was recommended in Europe as an alternative hypnotic for severe medical patients or aged patients, and chloral hydrate was considered as the hypnotic of choice in clinical trials of other psychotropic drugs in the United States and some other countries. Thus, a proper knowledge of the clinical effects, the side-effects, and the partial contraindications of

benzodiazepines resulted in the prescription of lesser-known alternatives, which were potentially less effective and more dangerous. This paradoxical prescription pattern may be named the ostrich effect.

The ostrich effect may be strengthened by official regulations. When New York's triplicate prescription policy began in January 1989, the following substitutional prescriptions increased: meprobamate, methyprylon, butabarbital, hydroxyzine, chloral hydrate, buspirone and fluoxetine.[33] Only buspirone seemed a justified choice at that time, although later research has proven that fluoxetine is also effective in the treatment of anxiety. When triazolam use was restricted in Spain in January 1992, three of the five hypnotic drugs whose use increased most had only recently been marketed in Western countries. As De Abajo pointed out:[29] 'These new hypnotics are not free from the psychiatric and memory disturbances that were responsible for the regulatory actions against triazolam'.

The increased use of antidepressants for treating insomnia may be another example of the ostrich effect. The National Disease and Therapeutic Index (NDTI) provides information about the treatment patterns of office-based physicians in the continental United States. The NDTI's analysis over the years 1987–1991 revealed a 10% decline in the use of benzodiazepines and a 100% increase in antidepressants for the treatment of insomnia.[19] This choice may seem adequate for new antidepressants, but is doubtful for tricyclics, such as amitriptyline. Furthermore, the hypnotic effect of antidepressants on non-depressed patients is practically unknown. Few antidepressants have been studied using the sleep tests generally administered in hypnotic research, such as the Multiple Sleep Latency Test, DISCAN scales for quality of sleep, diurnal sedation, etc. According to Walsh and Engelhart:[19] 'Thus, until the appropriate studies are conducted to determine hypnotic efficacy and safety and side effect profiles for the various antidepressants, their use for the symptomatic relief of insomnia has no scientific or clinical advantage over use of the benzodiazepine hypnotic compounds'.

From the 1970s onward, various experts in psychopharmacology and different government offices suggested that benzodiazepine consumption was too high in Western countries. These considerations were based on the total number of prescriptions, without taking into consideration other relevant factors, such as the prevalence of insomnia (20–30%)[34] and anxiety disorders (16%);[35] the deterioration in quality of life, function, accident rates, and disabilities associated with these disorders; and the high social and economic costs of anxiety and (probably) insomnia.

The fact is that consumption fell significantly in the majority of the market economies from the mid-1970s on. The restriction and stigmatization of benzodiazepines was promoted by the governments themselves, including the triplicate prescription forms that New York made obligatory in 1988,[33] or the regulations that the UK's Committee on the Safety of Medicines put into effect in 1988 and 1991. The latter set off an avalanche of malpractice suits in that country, based on lack of information regarding dependency risks, which were later dismissed. Dement had previously commented on the lack of common sense and disregard for current primary assistance practices shown by such recommendations.[32]

Public opinion, the mass media, and the attitudes and beliefs of certain health opinion leaders and government offices had already stigmatized this family of drugs even before Dr Van der Kroef's article appeared in 1979. The scapegoat effect is named for an expression used by Nino-Murcia[36] to describe triazolam's worldwide problems, trying to explain how its consumption had been influenced more by the accumulation of anecdotes than by scientific evidence. He commented on the need to study this case from a socioanthropological point of view. It is curious to note that the precise meaning of the Greek word *pharmakon* is 'scapegoat'.

COMMENTS

The case of Halcion is not an exception in psychopharmacology. The commercial history of fluoxetine[7,13] also illustrates the importance of the media effect, whereas the history of clozapine[14,37] provides a good example of other modifiers such as the Hawthorne and the Oedipus effects. MAOIs and lithium are other cases to be taken into consideration.

Psychosocial aspects have played an important role in the prescription and in the response patterns of some drugs; therefore, pharmacoepidemiologists need to become familiar with these effects, and manage adequately some concepts of psychosocial medicine which are relevant to the field (e.g. stigma, attitude, information and health

beliefs). Commercial case studies of drugs may contribute to the identification, description and understanding of psychosocial prescription and response modifiers. Operational definitions and a tentative classification of these effects may enhance their understanding on the part of specialists and health authorities. It may also contribute to the attenuation of these effect modifiers in the future.

REFERENCES

1. Shapiro, A. K. and Morris, L. A. The placebo effect in medical and psychological therapies. In: *Handbook of Psychotherapy and Behaviour Change* (2nd edn). Garfield, S. L. and Bergin, A. E. (Eds) Wiley, New York, 1979, pp. 369–410.
2. Grunbaum, A. The placebo concept in medicine and psychiatry. *Psychological Medicine* 1986; **16**: 19–38.
3. Blanz, M. Placebos: Aspects in medical history and approaches to definition. *Fortschritte der Neurologie-Psychiatrie* 1991; **59**: 361–370.
4. Kaada, B. Nocebo: The antipode to placebo. *Nordisk Medicine* 1989; **104**: 192–198.
5. Shepherd, M. The neuroleptics and the Oedipus effect. *Journal of Psychopharmacology* 1990; **4**: 131–135.
6. Sacristan, J. A., Soto, J. and Alanis, A. Complacency bias in clinical trials. *Lancet* 1992; **340**: 375.
7. Salvador-Carulla, L. and Leonsegui, I. Efectos psicosociales en farmacologia: ¿Algo mas que una anecdota? *Medicina Clinica* (*Barcelona*) 1995; **105**: 464–469.
8. Gregory L (Ed.). *The Oxford Companion to the Mind*. Oxford University Press, New York, 1987, p. 303.
9. Peck, C. and Coleman, G. Implications of placebo theory for clinical research and practice in pain management. *Theoretical Medicine* 1991; **12**: 247–270.
10. Goodwin, J. S. and Goodwin, J. L. The tomato effect: Rejection of highly efficacious therapies. *Journal of the American Medical Association* 1984; **251**: 2387–2390.
11. Hertzman, M. ECT and neuroleptics as primary treatment for schizophrenia. *Biological Psychiatry* 1992; **31**: 217–220.
12. Rothschild, A. J. Disinhibition, amnestic reactions, and other adverse reactions secondary to triazolam: A review of the literature. *Journal of Clinical Psychiatry* 1992; **53** (12 Suppl.): 10–17.
13. Ioannou, C. Media coverage versus fluoxetine as the cause of suicidal ideation. *American Journal of Psychiatry* 1992; **149**: 4.
14. Healey, D. Psychopharmacology and ethics of resource allocation. *British Journal of Psychiatry* 1993; **162**: 38–42.
15. Jonas, J. M., Coleman, B. S., Sheridan, A. Q. and Kalinske, R. W. Comparative clinical profiles of triazolam versus other shorter-acting hypnotics. *Journal of Clinical Psychiatry* 1992; **53** (12, Suppl.): 19–31.
16. Van der Kroef, C. Reactions to triazolam (letter). *Lancet* 1979; **ii**: 256.
17. Lasagna, L. The Halcion story: Trial by media. *Lancet* 1980; **i**: 1815–1816.
18. Ministerio de Sanidad y Consumo de España. *Guia farmacologica para la asistencia primaria*. Ministerio de Sanidad y Consumo, Direccion General de Farmacia y Productos Sanitarios, Madrid, 1987, p. 122.
19. Walsh, J. K. and Engelhart, C. L. Trends in the pharmacologic treatment of insomnia. *Journal of Clinical Psychiatry* 1992; **53** (12 Suppl.): 10–17.
20. Wysowski, D. K. and Baum, C. Outpatient use of prescription sedative–hypnotic drugs in the United States, 1970 through 1989. *Archives of Internal Medicine* 1991; **151**: 1779–1783.
21. Adam, K. and Oswald, I. Unpublished manufacturers research unfavourable (letter). *British Medical Journal* 1993; **306**(6890): 1475–1476.
22. Farid, B. T. and Bulto, M. Benzodiazepine prescribing (letter). *Lancet* 1989; **ii**: 917.
23. Blashfield, R. K. "Feighner *et al*., invisible colleges, and the Matthew effect". *Schizophrenia Bulletin* 1982; **8**: 1–12.
24. Kales, A., Scharf, M. B. and Kales, J. D. Rebound insomnia: a new clinical syndrome. *Science* 1978; **201**: 1039–1041.
25. Kales, A., Soldatos, C. R., Bixler, E. O. and Kales, J. D. Early morning. insomnia with short-acting benzodiazepines. *Science* 1983; **220**: 95–97.
26. Jonas, J. M. Idiosyncratic side effects of short half-life benzodiazepine hypnotics: Fact or fancy? *Human Psychopharmacology* 1992; **7**: 205–216.
27. Ellenberg, J. H. and Nelson, K. B. Sample selection and the natural history of disease. Studies of febrile seizures. *Journal of the American Medical Association* 1980; **243**: 1337.
28. Baldessarini, R. J., Finklestein, S. and Arana, G. Predictive power of diagnostic tests. In: *Psychobiology and Psychopharmacology*. Flach, F. (Ed.) Norton, New York, 1988, pp. 175–189.
29. De Abajo, F. J., Serrano–Castro, M. A., Montero, D., Rayon, P., Madurga, M. and Palop, R. Triazolam regulatory measures in Spain. *Lancet* 1993; 341: 185–186.
30. Schneider, P. J. and Perry, P. J. Triazolam: An 'abused drug' by the lay press? *DICP Annals of Pharmacotherapy* 1990; **24**: 389–392.
31. Meinzinger, M. M. and Barry, W. S. Prospective study of the influence of the media on reporting medical events. *Drug Information Journal* 1990; **24**: 575–577.

32. Dement, W. C. The proper use of sleeping pills in the primary care setting. *Journal of Clinical Psychiatry* 1992; **53** (12, Suppl.): 50–56.
33. Weintraub, M., Singh, S., Byrne, L., *et al*. Consequences of the 1989 New York State triplicate benzodiazepine prescription regulations. *Journal of the American Medical Association* 1991; **226**: 2392–2397.
34. Rosekind, M. R. The epidemiology and occurrence of insomnia. *Journal of Clinical Psychiatry* 1992; **53** (6, Suppl.): 4–6.
35. Regier, D. A., Farmer, M. E. and Rae, D. S. The epidemiology of anxiety disorders: The Epidemiologic Catchment Area (ECA) experience. *Journal of Psychiatric Research* 1990; **24** (2, Suppl.): 3–14.
36. Nino-Murcia, G. Discussion: New epidemiological findings about insomnia and its treatment. *Journal of Clinical Psychiatry* 1992; **53** (12, Suppl.): 40–41.
37. McKenna, P. J. and Bailey, P. E. The strange story of clozapine. *British Journal of Psychiatry* 1993; **162**: 32–37.

