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Summary

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Authorities acting as scientific advisers of industry – are roles becoming confused?

The pharmaceutical industry is responsible for proving the efficacy, safety and quality of medicines, in other words, for planning and implementing the necessary studies. The US Food and Drug Administration (FDA) authority participates actively in developing medicines by means of giving advice, which is to some extent binding on both parties.

FDA controls the development cycles of medicines, and how the contents of their marketing authorisation applications evolve.

The need for product-specific advice has also been recognised in the European Union. In terms of Article 51 of Council Regulation 2309/93/EEC, the functions of The European Agency for the Evaluation of Medicinal Products (EMEA) include giving scientific advice. In practice, this function has been delegated to the Scientific Advice Review Group (SciARG) of the Committee for Proprietary Medicinal Products (CPMP). Furthermore, many national authorities, including the National Agency for Medicines in Finland, give advice on request. A major difference from the FDA procedure is that the initiative in asking for advice is always taken by industry, and the advice is not binding on either party. In the course of the advisory procedure, no standpoint is taken on whether the reports and investigations would suffice for marketing authorisation. Industry feedback on the advice given by the National Agency for Medicines and CPMP has been generally positive.

The pharmaceutical industry has the required pre-clinical and clinical expertise for proving the efficacy, safety and quality of medicines. Why, then, is the advice given by the authorities needed? General and field of therapy guidelines cannot comprehensively deal with all issues arising during research and development. The problems may concern pre-clinical research, the extent of clinical research, the target group, efficacy variables, end points, and the analysis of results. The companies asking for advice must have a definite motivation for the plan. The authority are asked to comment on the interpretation of guidelines, the scientific details of research plans, and to give advice on proposed changes of research plans. The advice may only be ignored on justified grounds.

From the pharmaceutical industry's viewpoint, the primary importance of the advisory service is to support the marketing authorisation process of a medicine. For the authority, the emphasis lies in protecting consumers' interests. When the authority advises industry to change its research plan, the underlying reason would be to have the medicine examined in such a way that sufficient information on its efficacy, safety and quality is made available for the marketing authorisation decision (positive or negative) to be based on. The need of scientific advisory services to prove the efficacy and safety of a new medicine in comparison to an existing, recognised therapy alternative is clearly emphasised more in the European Union than in the United States.

The questions of responsibility and liability of scientific advisory services should be clear-cut. The advice given should not be binding, and the activities should be transparent. If the advice given were binding, it might be construed as a precedent. Furthermore, if scientific advice were binding in nature, the significance of the advice could erode, as science and therapy practices develop further.

Regardless of advisory services, the pharmaceutical industry will continue to carry responsibility for developing medicines and for producing sufficient evidence.

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Summary

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Modern treatment of venereal diseases

There has been an increase in sexually transmitted diseases in Finland in recent years. The large increase in the number of new cases of chlamydia infection has caused particular concern. In 2000, a total of 11,731 reports of chlamydia infection were received by the register of infectious diseases at the National Public Health Institute (1). Most of the infections occurred in the 20–24 year old age group. New cases of gonorrhoea infection totalled 284, and syphilis 204. About 9% of first-time appointments at venereal disease out-patient departments involve condyloma and 4% involve genital herpes (2).

Chlamydia

The majority of chlamydia infections involve adolescents who are either symptom-free or exhibit only minor symptoms. The diagnostic methods in use nowadays are more sensitive and more acceptable to the patient than before, and only a small amount of first-void urine is required for their implementation (3). Modern methods based on the identification of nucleic acid also make targeted screenings for chlamydia possible, and have been found to be cost-effective (4). The group especially at risk of contracting chlamydia consists of young adults who have several sexual partners, have previously been infected with chlamydia and use the contraceptive pill (5).

To treat uncomplicated chlamydia a single dose of 1 g of azithromycin is easily administered at the appointment itself (6). Excellent compliance is achieved with single dose medication (7). Alternative treatment and treatment in the complicated cases especially should consist of tetracycline 500 mg x 3, doxycycline 100 mg x 2 or erythromycin 500 mg x 4 administered for a period of 7–10 days.

Giving guidance to the infection carrier, and to those possibly infected, on how to make an appointment and get treatment, is an essential part of good treatment practice in all venereal diseases and is, in fact, one of the duties of the physician treating the patient. The follow-up of infection, especially in the case of chlamydia, should be intensified to allow symptom-free carriers to be tracked down more effectively. The post-treatment control specimen of chlamydia should be taken until about 3–4 weeks after the treatment.

Gonorrhoea

Culture is still used in the diagnosis of gonorrhoea; it also allows for the assessment of sensitivity of gonococcus to antimicrobial treatment. Gonorrhoeal infection can also be detected from a urine sample by a nucleic acid detection method as in the case of chlamydia.

For the treatment of uncomplicated gonorrhoea, the most commonly used treatment is ciprofloxacin 500 mg x 1 (6), and 500 mg x 2 for the duration of one week for the complicated disease. The problem nowadays arises from strains of gonorrhoea originating mainly from the Far East, which are often resistant to quinolones (8). The alternative treatment then is ceftriaxone 250 mg as a single intramuscular dose. Ceftriaxone is also recommended for the treatment of gonorrhoea during pregnancy (6). When using the culture method, the cure of gonorrhoea infection is ascertained one week after the treatment, and when using the nucleic acid detection method this is carried out three weeks after the treatment.

Syphilis

The number of new syphilis infections increased significantly in Finland during the 1990s, mainly due to the epidemic prevailing in Russia (9). The detection of syphilis infection is made difficult by its long incubation period (3–4 weeks) and large variation in the range of symptoms, and often also by its lack of symptoms. Serology may still be negative when the first symptoms appear (10). The patients should be advised to seek appointments at specialists to establish the stage of the disease, introduce treatment and review the partner situation.

The primary treatment of syphilis is procaine penicillin 600,000 IU daily im. for 2 weeks at the primary and secondary stage, and for 3 weeks at later stages (6). The alternative is im. ceftriaxone 1 g x 1. The fall in the cardiolipin titre is monitored after 3, 6 and 12 months. Penicillin is also an effective treatment of syphilis during pregnancy.

Genital herpes

The most common cause of genital herpes is Herpes simplex virus type 2 (HSV-2), but nowadays about 20% of the infections are caused by HSV-1. Of the Finnish adult population 70% is HSV-1 positive and about 20% HSV-2 positive (11). Only a proportion of those infected show typical symptoms of herpes and about half the infections are con-

tracted from a symptom-free partner or a partner unaware of his or her infection (12).

Antiviral drugs will not kill the virus but they can prevent its spread (13). The aim of drug treatment is to relieve the symptoms and prevent or shorten the duration of attacks, and thereby prevent others from becoming infected. The three drugs aciclovir, famciclovir and valaciclovir differ in dosage and price (6,14). The treatment can be divided into treatment of attacks and short and long-term prophylaxis. The initial attack may be an aggressive and long-term general infection, and antivirals will shorten the period of virus secretion from 12 days to 9 days. Antiviral treatment is given for 5–10 days. Reinfections are usually of shorter duration and associated with milder symptoms. The need for treatment is individual but to achieve the best possible response treatment should be initiated immediately at the onset of the first symptoms.

Short prophylactic treatment can be used e.g. during holidays in which case it is best to start the treatment about a week before the journey. Long-term prophylactic treatment can be offered to patients with frequently recurring herpes or herpes associated with awkward symptoms. In prophylactic treatment the dose can be adjusted individually according to the response, but usually aciclovir 400 mg x 2, famciclovir 250 mg x 2 or valaciclovir 500 mg x 1 is adequate. The duration of treatment varies from months to years. Symptom-free virus secretion can be reduced by prophylactic medication and thereby diminish the possibility of infecting others (15).

Condyloma

Condyloma is caused by human papilloma viruses. Only a fraction of those infected with a virus are found to have microscopic warts in the genital area (16). The diagnosis is mainly based on the typical clinical picture. The treatment is aimed at removing the visible changes, but the actual virus cannot be eradicated from the body. The choice of treatment is influenced by several factors, e.g. the location, size and number of the warts, the level of equipment of the clinic, the patient's opportunity to attend appointments for treatment and the price of treatment. There are several alternative treatments for condyloma, varying from topical treatment to surgery, and the treatment results are very variable. Relapses of the condyloma are the problem in all treatments (6). Many patients go through all the alternative treatments during their therapy.

The patient self can apply a podophyllotoxin solution (0.5%) or ointment (0.15%) on the warts on three consecutive evenings a week or with imiquimod ointment (5%) on three days a week (6,17). A precondition is that the patient should be capable of distinguishing the changes of warts from the normal skin and mucous membrane. The out-patient care can still continue with weekly applications of podophyllin. Skin irritation may be a problem with these topical treatments. Nor are they appropriate for the treatment of condylomata during pregnancy.

Cryotherapy and laser treatments are mainly given at out-patient clinics. The problem with cryotherapy is the pain it inflicts, and there may be blisters developing in the treatment area which clear within 1 to 2 weeks. Laser treatment is given under local anaesthetic and the wound areas usually heal within a couple of weeks, but they do require follow-up treatment.

The treatment of condyloma in women involves regular PAP tests to detect any cell changes in the uterine cervix as early as possible. Patients with condyloma are advised to use a condom for 3–4 months after completion of treatment to prevent transmission of infection because the risk of relapse is at its highest during that period.

Conclusion

A sexually transmitted infection is found in 40,000 people in Finland every year. All sexually transmitted diseases may be symptom-free, or exhibit only minor symptoms but still be infectious. We have good diagnostic and effective treatment available for sexually transmitted diseases, but the number of infections detected annually is nevertheless on the increase. It is therefore important to improve the guidance given to infection carriers and those exposed to infections by prompting them to be present at appointments for examination and treatment, and aiming especially at controlling the chlamydia epidemic in young adults.

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Summary

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Changes in the consumption of antipsychotics

Antipsychotics are used for the treatment of psychosis and of behavioural symptoms comparable to psychosis in severity. Other uses include the treatment of symptoms of alcohol and drug abuse withdrawal and states of confusion, restlessness and aggressiveness among the elderly and mentally retarded. The use of antipsychotics as hypnotics or for the treatment of anxiety or non-psychotic affective syndrome should be avoided (1).

Antipsychotics are divided into two groups: the conventional antipsychotics and the more recent type of second-generation antipsychotics. The earliest second-generation antipsychotics were introduced on to the market in the 1970s (1,2).

The second-generation antipsychotics may be considered as primary drugs in patients who have schizophrenic psychosis for the first time (1). They cause fewer adverse effects bearing on the quality of life of the patient than do conventional antipsychotics, and this has a positive effect on the patient's compliance (1,2).

One of the oldest second-generation antipsychotics, clozapine, is indicated for patients who have not responded to, or do not tolerate, other antipsychotics. Its use is associated with a risk of agranulocytosis, and therefore the blood count must be regularly monitored during treatment. Clozapine is considered the best of the second-generation antipsychotics, but newer second-generation antipsychotics have less bone marrow toxicity (3). Risperidone and olanzapine were introduced in the mid 1990s (2)and the latest quetiapine was launched on the market in 2000.

The consumption of antipsychotics has remained relatively steady during the 1990s (Fig. 1). A slight increase may be perceived since 1998, but the total consumption in 2000 (14.21 DDD/1,000 inhabitants/day) is nevertheless slightly lower than in 1990 (14.77 DDD/1,000 inhabitants/day). The consumption of second-generation antipsychotics has increased during the entire 1990s at the same time as the consumption of conventional antipsychotics has dropped (Figs. 1 and 2). The increase in the consumption of second-generation antipsychotics is partly explained by the introduction on to the market olanzapine, risperidone and quetiapine. The most significant decrease in consumption (48%) among conventional antipsychotics has occurred with thioridazine, thioproperazine and periciazine (Fig. 1).

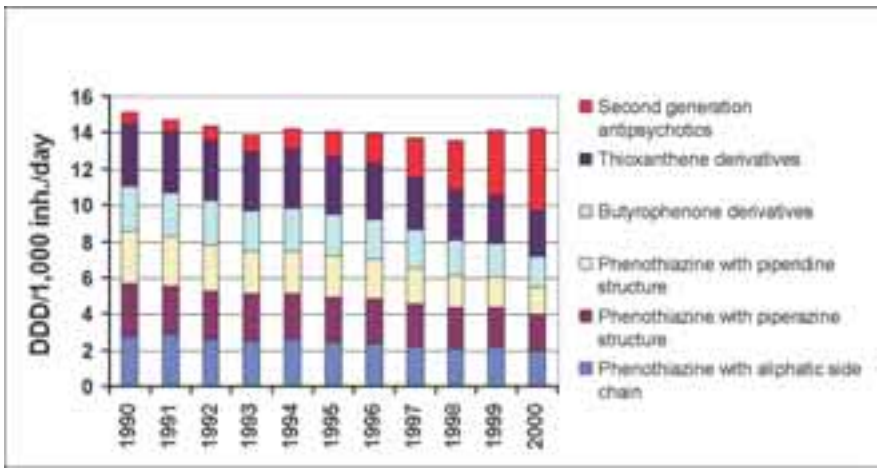
The most frequently used second-generation antipsychotics are olanzapine, risperidone and clozapine (Fig. 2). Three- or four-fold increase in the consumption of olanzapine and risperidone has occurred within the past few years, but the consumption of clozapine has increased moderately. The consumption of sulpiride has dropped by about 40% since the beginning of the decade.

According to current therapeutic practice, the aim is to treat patients with psychosis in out-patient care (4). The use of antipsychotics is considerably higher in out-patient care compared with treatment in institutional care (Figs. 3 and 4). The number of available beds in psychiatric specialist in-patient care has decreased steadily when patients have been transferred from institutional to out-patient care. The length of periods in institutional care have also been shortened (4).

The increase in the out-patient consumption of second-generation antipsychotics has been significantly higher than that in in-patient institutional care (Fig. 3). This is explained by the introduction of therapies with second-generation antipsychotics (with the exception of clozapine).

The consumption of conventional antipsychotics has dropped, par-

Fig. 1. Total consumption of antipsychotics.



ticularly in institutional care (Fig. 4). The decreased use of institutional care may partly be due to the therapeutic practice which promotes out-patient care and the use of more recent second-generation antipsychotics. The consumption of conventional antipsychotics in out-patient care has decreased only slightly because their use has probably been continued in patients who have responded well to the drug they have been using (1).

Among the aliphatic phenothiazines generally used in out-patient care, the consumption of chlorpromazine has decreased (Fig. 5), the consumption of levopromazine has varied (Fig. 6) and the consumption of promazine has increased in the 1990s (Fig. 7). The use of promazine in institutional care has remained steady, but its consumption in out-patient care has increased. Promazine and levopromazine have been used as hypnotics in the non-psychotic elderly (1, 5). This exposes the patient to the extrapyramidal and anticholinergic adverse effects of these drugs, and therefore antipsychotics should not be used as hypnotics without any other psychiatric indications (1). However, based on the increased out-patient consumption it can be assumed that promazine and levomepromazine have possibly been used even for other psychotic symptoms more frequently than other neuroleptic agents (Figs. 6 and 7). In 1999, the most common drug causing fatal intoxication was levomepromazine and the third most common drug was promazine (6). According to Vuori (2000), the underlying cause of a great proportion of the fatal intoxications with promazine was alcohol, and it appears that antipsychotics, especially promazine, are increasingly more commonly prescribed as sedatives and sleep aids for alcohol abusers in lieu of benzodiazepines. The absence of small pack sizes and negligence in following the instructions for dosage can lead to fatal results in alcohol abusers accustomed to less toxic benzodiazepines (7). In view of information revealed by the consumption data it may also be appropriate to consider the availability of smaller

Fig. 2. Consumption of the second generation antipsychotics.

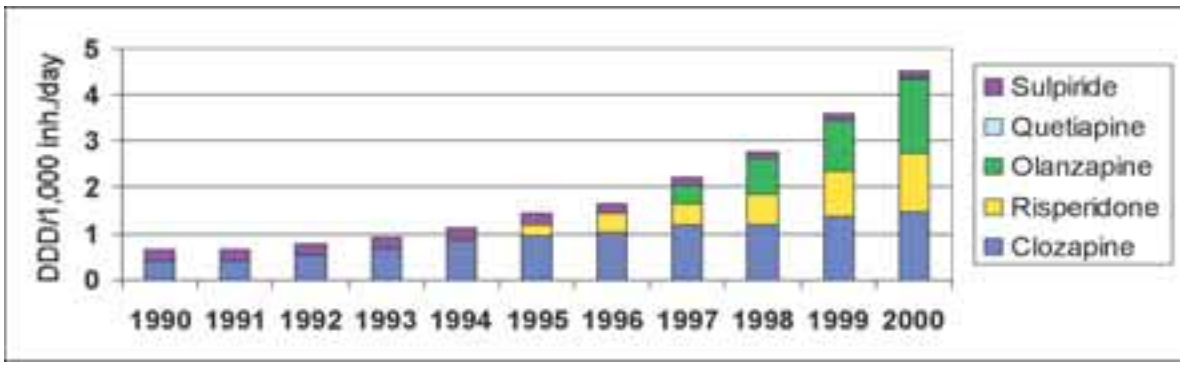


Fig. 3. Consumption of the second generation antipsychotics.

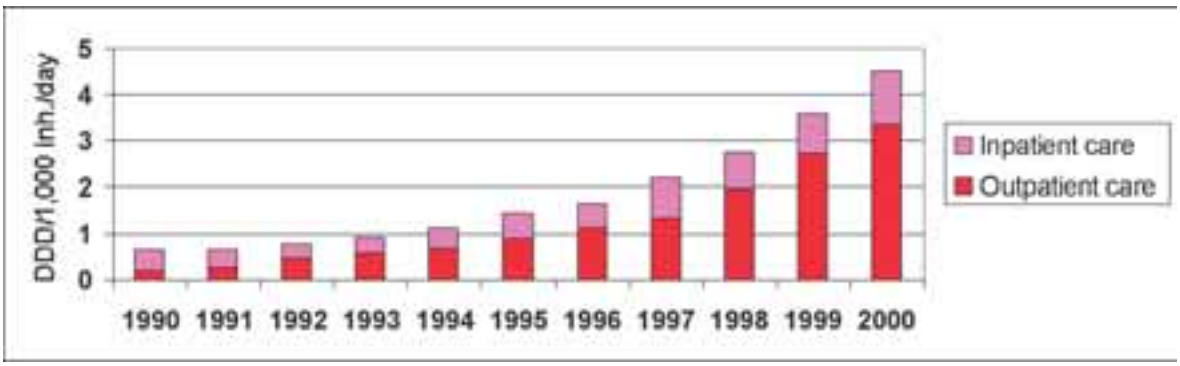
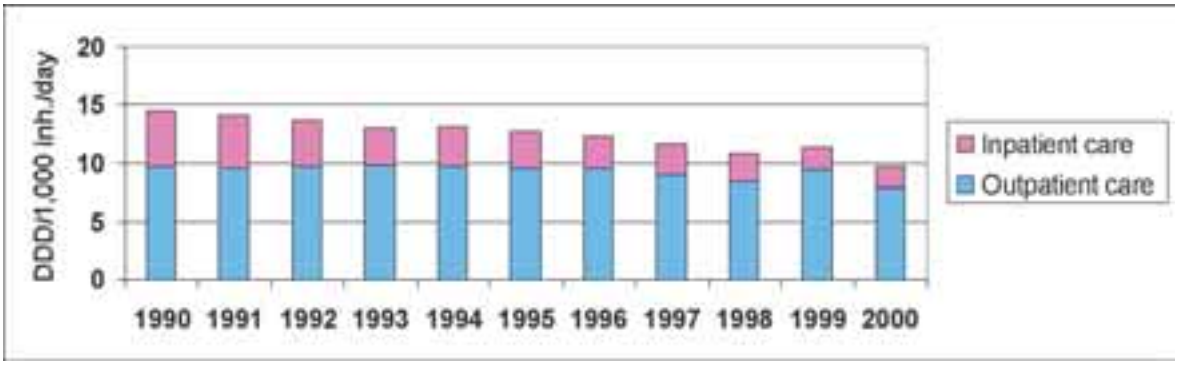


Fig. 4. Consumption of the conventional neuropleptics.



pack sizes and to check the therapeutic indications.

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Translation Mervi Moisander

Fig. 5. Consumption of chlorpromazine.

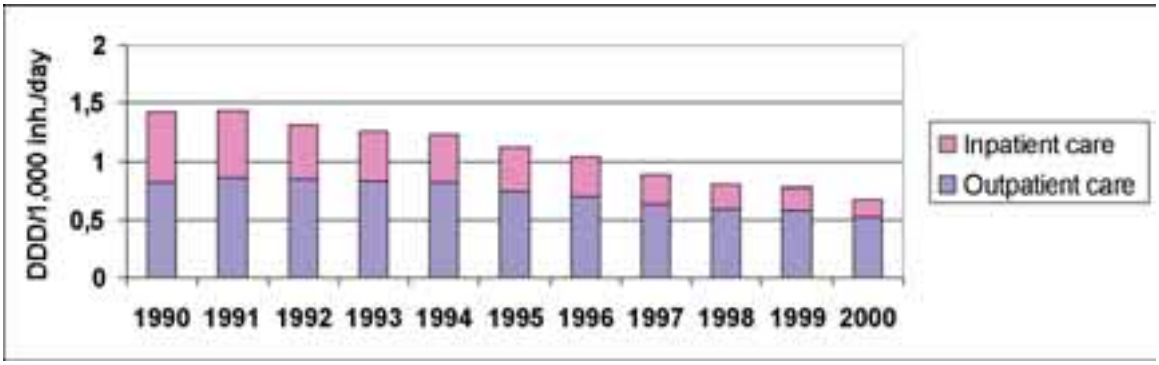

Fig. 6. Consumption of levomepromazine .

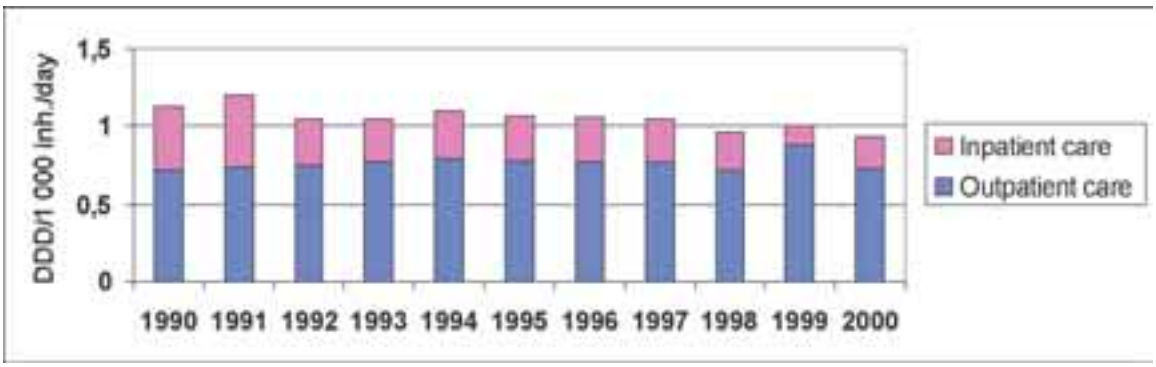

Fig. 7. Consumption of promazine.