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Article

What is behind the seeming cessation of the increase in sleep medicine consumption in Finland during the last years?

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Significance for public health

Insomnia and sleeplessness are increasingly recognized as a public health concern in contemporary Western societies. The official guidelines for insomnia treatment in Finland have been constantly striving for a decline in the use of sleep medication for long-term insomnia treatment. During recent years there has been a gradual decrease in the annual consumption of sleep medication. Thus, one would think that the measures endorsed by the guidelines have been successful. However, the situation is more complicated. The decrease in traditional hypnotic use may be partly misleading. There seems to be a current and continuing trend in outpatient care to increasingly replace traditional hypnotics with subclinical doses of some other drugs not originally developed for insomnia treatment, including antidepressives, antipsychotics and antiepileptics. The long-term consequences of this practice are unknown and therefore a potential public health concern.

Abstract

In Finland, between 2003 and 2010 and parallel to the increase in the prevalence of insomnia-related symptoms among the general population, there has been a cessation of growth and even a decrease in the consumption of traditional hypnotics. The reasons behind this seemingly paradoxical situation are not known. We analyzed trends over the period 2000-2010 in the estimated consumption of traditional hypnotics and some new drugs that are destined for use in insomnia treatment. We used the annual wholesale statistical database compiled by the Finnish Medicine Agency, FIMEA, and data from the Finnish Drug Prescription Register. We found evidence to support two parallel trends in Finnish outpatient care. First, there seems to be a trend in which physicians increasingly comply with official guidelines for insomnia treatment, which partly accounts for the decrease in the consumption of traditional hypnotics. Second, at the same time, the first trend seems to be resulting in an increasing trend to treat insomnia patients with some new drugs that were not originally developed for insomnia treatment by prescribing these non-hypnotic drugs in small, sub-clinical doses. The current trend in practice may have contradictory effects on the treatment of insomnia. The long-term consequences of using low doses of drugs other than hypnotics to treat insomnia are not known and the situation should, therefore, be followed-up in subsequent studies. However, pharmacological treatment should never be a substitute for non-pharmacological treatments of insomnia.

Introduction

In Finland, between the years 1972 and 2005, occasional insomnia-related symptoms have increased, especially among the employed and working age population.[1] The same study also found evidence of a possible smaller increase in chronic insomnia-related symptoms over the past ten years. In addition, our unpublished results indicate a continued increase in the same symptoms in the years after 2005 (*E. Kronholm, unpublished results, 2009*). The potential health implications of these trends may be important. Recent studies have found that Insomnia-related symptoms predict future morbidity and mortality,[2-5] as well as disability retirement.[6-10] In addition, insomnia and insomnia-related symptoms precede depression and insomnia may be a risk factor for this; but the association may also be bi-directional.[11-17]

In clinical practice, the long-term treatment of insomnia is often largely based on sleep medication, in spite of guidelines to the contrary.[18,19] Although short-term hypnotic treatment has been demonstrated to be effective, a substantial proportion of patients have proven to be resistant to the treatment or do not gain much benefit.[19] In addition, there is increasing evidence to suggest that the use of sleep medicine has been associated with serious health risks.[20-22] Therefore, the question regarding the long-term pharmacological treatment of chronic insomnia, at least in Europe, is unresolved and urgently needs to be answered.[23]

In Finland, in parallel with the increase in the prevalence of insomnia-related symptoms among the general population, there has been a significant increase in the consumption of hypnotics (ATC code N05C). Between the years 1975 and 2005, the consumption of hypnotics has increased 2.8-fold.[1] However, beginning in the year 2004, there has been a halt in the increase in the consumption of hypnotics and this has even started to decline. The reasons behind this decrease are unclear. One possibility is that physicians in clinical practice have begun to demonstrate greater compliance with the instructions given by the official guidelines for insomnia treatment. However, there is also another possible explanation.

Recent years have seen an ongoing discussion among Finnish sleep specialists. This could be the result of an increasing condemnation of the long-term use of hypnotic medication and, for this and other such reasons, increasing numbers of clinical practitioners in Finland may have begun prescribing antidepressants and other drugs instead of hypnotics to treat insomnia. When used to treat insomnia, the doses for these drugs are, in general, much lower than the *official indication* for a given drug. We decided to explore the trends in the sale of traditional hypnotics (ATC code N05C) and in the sub-clinical doses for antidepressives (N06A), as well as antipsychotics (N05A) and an antiepileptic drug (pregabalin) during the time period when the

increase in the consumption of traditional hypnotics had stopped and even begun to decline, but when a parallel increase in the prevalence of insomnia-related symptoms among the general population has also taken place.[1] We hypothesized that the use of medication for insomnia has, in reality, not decreased, but that the increase in the use of traditional hypnotics has been replaced by sub-clinical doses of antidepressants and other drugs.

Design and Methods

Data sources

We used an annual wholesale statistical database compiled by the Finnish Medicine Agency, FIMEA.[24] The figures in the database represent the volume of sales to pharmacies and hospitals by the two largest drug wholesalers in Finland, which together account for nearly 100% of total national drug sales. The remaining sales (approximately 1%) are mainly hospital sales. The statistics include preparations registered for human use in outpatient care and in institutions.

The database lists drugs according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System[25] and calculates the consumption of such drugs using the assumed average maintenance dose per day for each drug according to its main indication for adults. The consumption is expressed as Defined Daily Dose (DDD) per 1000 inhabitants per day. At the end of 2010, the Finnish population was 5.38 million.

Analysis of drug consumption

Using the above-mentioned data source, we analyzed trends during 2000-2010 in the consumption of traditional hypnotics (N05C), antidepressives (N06A), an antiepileptic drug (pregabalin, N03AX16), and antipsychotics quetiapine (N05AH04) and levomepromazine (N05AA02) by different tablet strengths. We chose the drugs based on clinical experience and published recommendations.[26] That is, we included in our study the drugs generally believed to be widely used to promote sleep in Finland. Several national recommendations have been published on the treatment of insomnia,[27] but it is still unknown whether or not clinical practice is in line with these guidelines.

We reasoned that if a drug with tablets of several strengths and a main indicator other than insomnia was consumed in a low tablet strength (that is used with a daily dosage well below the recommended therapeutic maintenance dosage range for its main indication), it was considered to be most likely used for the treatment of insomnia. The reasoning for using these particular tablet strengths and drug doses was also based on clinical experience and general information on the doses commonly used by clinicians in everyday practice for treating insomnia. Table 1 shows drugs destined for use in promoting sleep in place of traditional hypnotics, the strength of the tablets for sale, the typical number of doses in the main indication, and when they are supposed to be taken as a hypnotic.

The annual number of individuals who purchased N05C drugs was derived from the Finnish Drug Prescription Register. All drugs prescribed by physicians to outpatients and reimbursed by the national Health Insurance Scheme are included in the Finnish Drug Prescription Register, which was established in 1993 and is maintained by the Social Insurance Institution of Finland.[30]

Results

Figure 1 shows trends in the annual total consumption of traditional hypnotics (N05C) from 1990 to 2010. The combined consumption of traditional hypnotics in outpatient and institutional care increased almost every year between 1990 and 2003 (from 35.1 to 55.9 DDD/1000 inhabitants/day, respectively). After 2003, the consumption of these drugs began to decline: by 2010, the level of consumption was 49.1 DDD/1000 inhabitants/day. The total decrease was 6.8 DDD/1000 inhabitants/day (12.2%). When we analyzed the annual consumption for outpatient care only, the number decreased from 50.8 to 47.0 DDD/1000 inhabitants/day between 2003 and 2010. Thus, the total decrease was 3.8 DDD/1000 inhabitants/day (7.5%). Consequently, the total decrease in institutional care was 3.0 DDD/1000 inhabitants/day (58.8%).

In outpatient care, increasing trends in the annual consumption of the drugs under study according to different tablet strengths were observed (Figure 2). We found the most striking increase in the consumption of the antidepressant mirtazapine (tablet strength 15 mg). Between 2002 and 2010, the level of consumption of this drug increased from 0.03 to 2.4 DDD/1000 inhabitants/day. It accounted for 61% of the total increase in the use of this drug. We found the next highest increase in the consumption of the antidepressant amitriptyline (10 mg and 25 mg). Between 2000 and 2010, the level of consumption of

Table 1. Some drugs that are destined for use in Finland (2000-2010) to promote sleep instead of traditional hypnotics (N05C).

Generic name of drug	ATC code	Strength of tablets (mg) in Finland	Strength of therapeutic dose (mg/d) for main indication	Strength of dose (mg/d) for insomnia treatment
Amitriptyline	N06AA09	10; 25; 50	50-75 (pain)[24] 150-300 (depression)[24]	10-25 (max 50)[24]
Doxepin	N06AA12	10; 25; 50	75-150 (ad 300)[24]	1-10; 10-25 (max 50)[24]
Mianserin	N06AX03	10; 30; 60	60-90 (ad 120)[24]	10-30
Trazodone	N06AX05	50; 100	150-300 (ad 600)[24]	25-100[24]
Mirtazapine	N06AX11	15; 30; 45	15-45	3.75-7.5 (15)[27]
Levomepromazine	N05AA02	5; 25; 50; 100	ad 750[24]	5-100[24]
Quetiapine	N05AH04	25; 50; 100; 200; 300; 400	300-450 (schizophrenia)[24] 200-800 (bipolar affective disorder)[24]	25-100[28]
Pregabalin	N03AX16	25; 75; 150; 225; 300	150-600 (epilepsy, neuropathic pain, and generalized anxiety disorder)[29]	25-50°

°Based on clinical practice, no published sources available.

this drug increased from 1.33 to 1.95 DDD/1000 inhabitants/day. Notably, these figures accounted for 87% of the total increase in the use of amitriptylin; the use of 50 mg tablets accounted for only a 13% increase in the level of consumption. Consumption of the antipsychotic drug quetiapine (25 mg) increased from 0.02 to 0.53 DDD/1000 inhabitants/day. The increase in the use of small doses (25 mg, 50 mg, and 100 mg) of quetiapine accounted for 38% of the total increase in the use of this drug. Notably, use of a new antiepileptic drug called pregabalin (25 mg) increased from 0.02 to 0.21 DDD/1000 inhabitants/day between the years 2003 and 2010. This represents a remarkable 10-fold increase in the level of consumption of the sub-clinical strength of the drug within eight years. Other non-hypnotics considered to have been used for insomnia treatment showed either a decreasing trend in the annual level of consumption of sub-clinical doses (mianserin 30 mg and doxepin 25 mg) or virtually no meaningful trend at all (levomepromazine 5 mg and 25 mg, and mianserin 10 mg) (Figure 3). Trazodone, which can be used for insomnia treatment also in its strongest tablet strength, did not show any meaningful trend in its consumption (0.14 DDD/1000 inhabitants/day in 2001 and 0.15 in 2010) and was, therefore, left out of further analyses and figures.

The decrease in the annual consumption of traditional hypnotics during the period 2003-2010 in outpatient care was 3.8 DDD/1000 inhabitants/day (Figure 1). At the same time, the total increase in the annual consumption of drugs other than ATC group N05C hypnotics, which are destined for use in the treatment of insomnia, was 3.2 DDD/1000 inhabitants/day, accounting for 84% of the total decrease in the consumption of traditional hypnotics.

Data from the Finnish Drug Prescription Register (Table 2) showed that the number of individuals who received reimbursement for N05C drugs increased between 2006 and 2009 by 61,540 individuals. Consequently, it can be inferred that the number of used doses per patient may have decreased during those four years. However, their number first started to decline in 2010 when a total of 356,192 outpatients requested reimbursement for at least one prescription of N05C

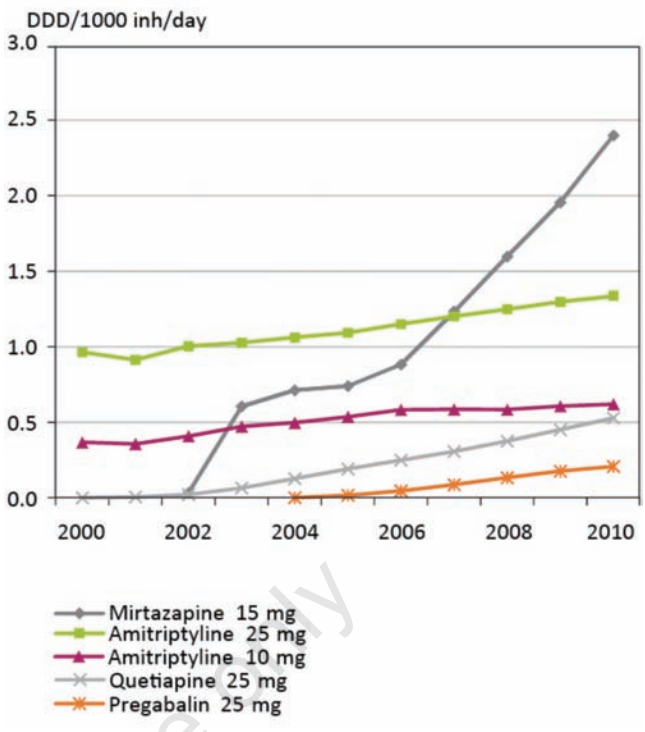

Figure 2. Increase in trends of annual consumption of sub-clinical doses of some antidepressants and other drugs supposedly used instead of hypnotics to treat insomnia in outpatient care.

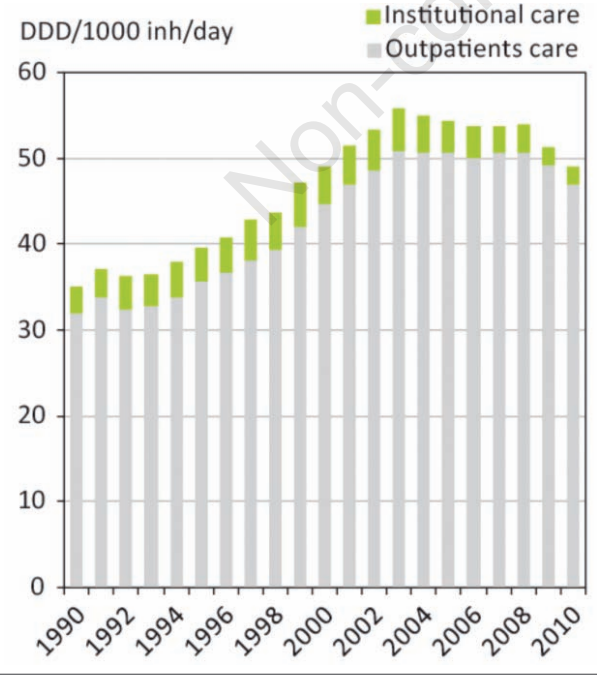

Figure 1. Trends in annual consumption of traditional hypnotics (ATC group N05C) (1990-2010).

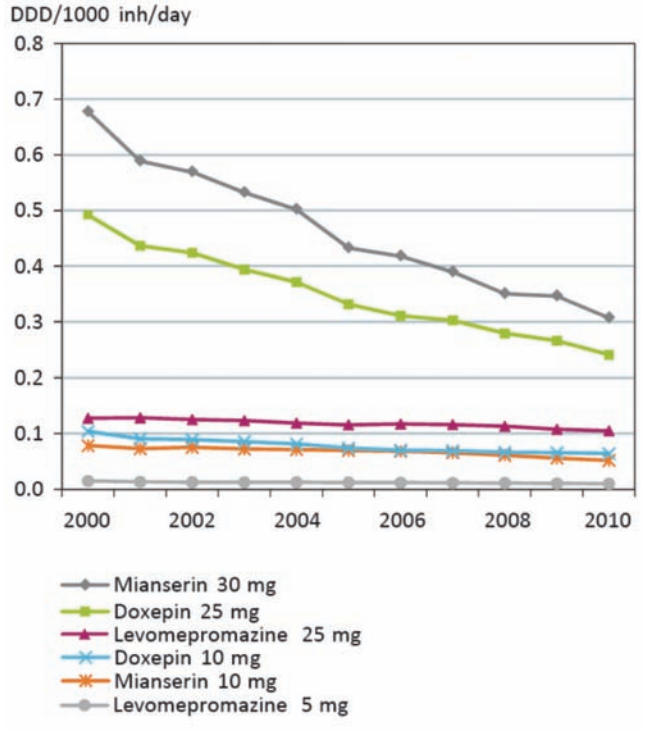

Figure 3. The decrease or absence of any trend in sub-clinical doses of other supposed substitutes of traditional hypnotics.

Table 2. Total consumption of hypnotics (in Defined Daily Doses, DDDs), as assessed according to the wholesale data and the Drug Prescription Register for N05C drugs used in outpatient care during 2005-2010.

Year	Total consumption of N05C drugs DDD (million)	Reimbursed consumption of N05C drugs DDD (million)	Coverage % of reimbursed consumption of N05C drugs from total consumption	N. of persons receiving reimbursement for N05C drugs
2005	96.9	66.7	68.9	252.684
2006°	96.5	73.9	76.5	308.331
2007	97.8	77.4	79.2	334.180
2008	97.4	77.6	79.7	342.073
2009	93.0	79.5	85.5	369.871
2010	87.5	75.4	86.2	356.192

°At the beginning of 2006, the method of calculating reimbursement payments in the Finnish insurance system changed. With the reform, the fixed non-reimbursable sum paid by the patient per purchase (≤10 euros) was abandoned. In the new system, the reimbursement payment is calculated separately for each medical product and almost every purchase of N05C drugs (with approved reimbursement status) can thereby be found in the drug prescription register.

drugs, resulting in a decrease of 3.7%. The register covered 86% of the total consumption of N05C drugs (assessed by wholesale DDDs) in Finnish outpatient care. The data from 2011 show a further decline (347,873 individuals in 2011, a decrease of 8319 individuals) when compared to 2010.

Discussion

The main finding of this study was that the apparent decrease in the annual use of sleep medication based on statistics for ATC group N05C hypnotics may be partially misleading. The consumption of traditional hypnotics has dramatically decreased in institutional care, but in outpatient care the decrease has most likely been caused by a shift in the prescribing practices of physicians in Finland. It is quite likely that, during the last few years, an increasing number of practitioners have replaced ATC group N05C hypnotics with sub-clinical doses of some ATC group N06A antidepressants (*i.e.* mirtazapine and amitriptyline) and some other drugs (*i.e.* the antipsychotic drug quetiapine and the antiepileptic drug pregabalin). This change in the treatment of insomnia seems to be continuing. It seems that the effort to decrease the use of sleeping medicine within the health care system[27] has not been as successful as one might have thought. There is a general lack of therapists in the Finnish health care system and most resources are channelled to the treatment of major psychiatric conditions. Only a few psychologists or physicians are trained to treat insomnia with Cognitive-Behavioral Therapy for insomnia (CBTi). Furthermore, to our knowledge and to the knowledge of the sleep specialists in Finland (*J. Markkula, personal communication, 2012*), there has been no major increase either in the use or training of CBTi in Finland during the past decades. Thus, the decrease in the use of hypnotics has not resulted in an increase in the use of cognitive and behavioral treatments for insomnia within the Finnish health care system. Rather, it has merely resulted in an apparent shift from one class of drugs to another. We were able to account for 84% of the total decline in the consumption of traditional hypnotics via a transition to the use of sub-clinical doses of mirtazapine, amitriptyline, quetiapine and pregabalin in outpatient care. There are some other drugs which are also probably used instead of the traditional hypnotics, but the purpose for which these drugs are used cannot be inferred from the tablet strength. Consequently, we may have slightly underestimated the full extent of the transition in drug use. However, the number of individuals who received reimbursements for traditional hypnotics has also increased by 20% between 2006 and 2009. Given that the total sales in outpatient care have decreased during the same period, this suggests that the number of doses of traditional hypnotics per patient has decreased and/or the duration of treatment has been shortened. In turn, this would suggest that physicians are increasingly demonstrating greater compliance with the guidelines for insomnia treatment. This increasing compliance to official guidelines by physicians may decrease the consumption of N05C drugs partly also by increased prescriptions for intermittent (non-nightly) use of traditional hypnotics, which has been suggested, although not generally accepted among clinicians, to be a possible strategy to prevent intolerance and maintain efficacy. This could explain part of the decrease in the consumption although the number of patients had increased. However, this possible trend could hardly account for the total decrease in N05C consumption. First, from Table 2 it can be calculated that the ratio of consumption of reimbursed DDD/year to the number of persons receiving reimbursement for N05C drugs has shown only a small decrease between 2006 and 2010, suggesting that the clinical practices among patients continuing to use N05C drugs remain relatively constant. Second, notably during the last two years there has been a decrease in the number of persons who have received reimbursement for N05C drugs at the same time as the consumption of sub-clinical doses of antidepressants and some other new drugs has increased. Given that the prevalence of insomnia-related symptoms has increased, it seems unlikely that the decrease in reimbursement figures of N05C drugs would reflect the increased prevalence of non-pharmacological treatment. On the contrary, availability of CBTi in Finland remains scarse. We are, therefore, inclined to conclude that there seem to be two parallel, probably interrelated, processes behind the decrease in the consumption of traditional hypnotics in outpatient care during the last seven years in Finland: physicians increasingly complying with the official guidelines for insomnia treatment and a shift from traditional hypnotics to other drugs not originally developed for insomnia treatment. Taken together, these trends suggest that a continuously increasing number of insomnia patients are treated with different drugs and that only a small part of the decrease in the use of traditional hypnotics can be explained by increased compliance with the official guideline instructions for insomnia treatment, which promote the use of non-pharmacological treatments for chronic insomnia. For the most part, the decrease in the use of traditional hypnotics seems to be explained by a shift to other types of drugs. Importantly, in addition to the possible health risks supposedly associated with the use of N05C group hypnotics,[22,31,32] the long-term consequences of the use of new antidepressants and epileptic and antipsychotic drugs in sub-clinical doses as insomnia treatment are known to also pose a risk.[26]

The strength of our study is that we had annual wholesale data from the outpatient care system at our disposal, including information on prescription and over-the-counter drugs, as well as reimbursed and non-reimbursed drugs or packages of the same drug. However, it should be noted that all target drugs in this study are available by prescription only, according to Finnish legislation. There are also limitations in our study which should be considered when interpreting the results. First, the study was based on public statistics, so we did not have access to patient-level data. Second, although the use of wholesale data can be considered

to be one of the strengths of the study, it should also be mentioned that some drugs sold may still be unused, either in pharmacies or in the patient's home. Third, we calculated the DDD figures in relation to the total population, even though the use of hypnotics is exceptional among children (about 1 million in Finland). Fourth, physicians recommend only using antidepressants in small doses to start with[33] and only using full clinical doses after a few weeks. This short transition period overlaps with the use of the given drug for insomnia treatment. If the total use of some antidepressant has shown a large increase, it would also have slightly increased its sale in small sub-clinical doses, making interpretation difficult. However, we found that the increase in the use of small sub-clinical doses of amitriptylin accounted for 86.5% of the total increase in the use of the drug, suggesting that the increase in the use of small sub-clinical doses is probably not explained by the general increase in the use of the drug for the treatment of depression. As a limitation of this conclusion it must, however, be admitted that we cannot exclude the possible effect of improper use of sub-clinical doses of antidepressants to treat depression which may have partly increased their use. However, we feel that it is unlikely that the practice of improper use of antidepressants would have become more common during the last decade given the amount of education and information given to health care professionals about the treatment of depression. In addition, a further limitation, regarding inferences on the causes of the increase in use of sub-clinical doses of amitriptylin, is that it is also used in low doses for pain relief, such as migraine[34] and irritable bowel syndrome.[35] However, the use of quetiapine and pregabalin for pain in low sub-clinical doses is most uncommon. The emergence of various new alternatives for pain management suggests that there may not have been much pressure to increase the use of antidepressants for pain management in Finland.

Conclusions

The results of this study suggest that the decrease in the annual use of traditional hypnotics is, for the most part, explained by a shift in the prescribing practices of physicians. Currently, insomnia is increasingly treated by small sub-clinical doses of antidepressants and some other new drugs. This means that such drugs are being used for purposes other than those for which they were originally developed. This practice should not prevent the treatment of insomnia via behavioral therapy and other recommended forms of non-pharmacological treatment, and their more general use in outpatient care. The long-term consequences of this practice are not known and, therefore, the situation should be followed-up with further study.

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