Selective serotonin reuptake inhibitors (SSRI) – sales, withdrawal reactions and how drug regulators reacted to this with benzodiazepines as comparator.

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1. Preface and acknowledgement

1.1 Structure of the thesis

This thesis follows the guidance for PhDs from the Faculty of Health Sciences, University of Copenhagen. First, I will present the context into which the three papers that this thesis consists of belong. Next, I will present the objectives of the thesis and the three papers, and the methods and results, which I will discuss in relation to each paper. The thesis will end with a conclusion and perspectives.

Before starting this PhD project, I used to work as a senior health advisor to the Danish Consumer Council and among other things also with medicines and the organisation around medicines. This involved registration of adverse drug reactions of some specific medicines, and among these benzodiazepines and selective serotonin reuptake inhibitors (SSRIs). This gave rise to several questions, e.g.:

- Why is the usage of newer antidepressants increasing so much and so fast
- Why are benzodiazepines considered addictive, while SSRIs are not
- What is the effect of the newer antidepressants
- What are the adverse effects of newer antidepressants
- What is the balance between benefits and harms
- What is the definition of depression

The thesis encompasses three scientific papers:

1. An analysis of psychotropic drug sales. Increasing sales of selective serotonin reuptake inhibitors are closely related to number of products. International Journal of Risk & Safety in Medicine, 2011; 23 (2): 125-32
2. What is the difference between dependence and withdrawal reactions? A classification and literature review of benzodiazepines and selective serotonin reuptake inhibitors. Addiction. 2011 Oct 12. doi: 10.1111/j.1360-0443.2011.03686.x. [Epub ahead of print]

3. Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did health authorities react?

1.2. Acknowledgements

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2. Abstract

Psychotropic drug use has increased in all European countries, also in Denmark, due to the introduction of the so-called selective serotonin reuptake inhibitors (SSRIs) in the late 1980s and changed prescription habits. Further, patients have raised the suspicion that the SSRIs could cause dependence. This suspicion has, however been rejected by marketing authorisation holders and by regulatory agencies, the latter being responsible for guarding public safety in relation to medicines

The overall aim of this PhD thesis was to explore the life-cycle of the SSRIs and compare it with benzodiazepines with respect to use and dependence. This was investigated in 3 studies. In the first study, we explored the possible causes for the sales of psychotropic medicines in Denmark. In the second study we explored the rationale for claiming that benzodiazepines cause dependence while selective serotonin reuptake inhibitors (SSRIs) do not. The third study was a documentary study describing actions and statements of the regulatory agencies in UK, USA, England and Denmark. We explored the communications from drug agencies to the public saying that benzodiazepines cause dependence whereas selective serotonin reuptake inhibitors (SSRIs) cause a withdrawal syndrome because the phraseology of the communications might explain why benzodiazepines are viewed as being addictive in contrast to SSRIs.

The first study showed that the sales of psychotropic drugs has fluctuated widely over a 37-year period. We believe that the decline in sales of benzodiazepines was primarily due to the recognition that they cause serious dependency and by initiatives at a national level to curb their use, and that the recent steep increase in sales of SSRIs is a direct consequence of marketing pressures, as the effect of the SSRIs is overestimated.
The second study showed the withdrawal reactions to SSRIs were very similar to those for benzodiazepines. It therefore makes no sense to describe only the latter as dependence symptoms. denied that the reactions indicated SSRI dependence. Drug regulators underestimated in both cases the frequency and severity of the symptoms. The third study showed that in the perspective of the precautionary principle it could be understood as if the drug agencies have refused to acknowledge that SSRIs can cause dependence, with reference to the diagnostic disease manuals ICD-10 and DSM-IV, and minimised the problem with regard to the severity and the number of people affected.

In this perspective changes in the communication from drug regulators to the public about adverse effects happened slowly.

In the perspective of the risk management principle it could be understood as if the drug agencies have reacted in concordance with the slow growing knowledge of adverse drug reactions and have sharpened the information to the public over time. However, relying on spontaneous reporting of adverse effects leads to underrecognition and delayed information about the problems.

3. Danish summary

Brugen af psykotropisk medicin er steget i alle europæiske lande, også i Danmark, på grund af markedsføring af de såkaldte selektive serotonin genoptagelseshæmmere (SSRI) i slutningen af 1980erne og deraf følgende nye vaner for udskrivning af medicin. Patienter har rejst mistanke om at SSRI præparater kunne medføre afhængighed. Denne mistanke er dog blevet afvist af markedsførings indehavere og lægemiddelmyndigheder.

Det overordnede formål med denne ph.d.afhandling var at undersøge SSRI´ernes livscyklus og sammenligne med benzodiazepinerne med hensyn til forbrug og afhængighed. Dette blev undersøgt i tre studier. I det første studie undersøgte vi mulige forklaringer på salget af psykotropisk medicin i Danmark. I det andet studie undersøgte vi rationalet for påstanden om at benzodiazepinerne kan forårsage afhængighed, mens SSRI´erne ikke kan. Det tredje studie var et dokument studie, som beskrev initiativer og udtalelser fra lægemiddelstyrelserne i USA, Storbritanien og Danmark samt det europæiske lægemiddelagentur. Vi undersøgte kommunikationen mellem lægemiddelmyndighederne og offentligheden i relation til om benzodiazepiner kunne medføre afhængighed mens SSRIerne kunne medføre ophørsproblemer, fordi udtryksmåden kunne bidrage til at forklare, hvorfor benzodiazepinerne betragtes som afhængighedsskabende i modsætning til SSRI´erne.

Det første studie viste at salget af psykotropiske lægemidler varierede meget over en 37 årig periode. Det er vores opfattelse, at faldet i salget af benzodiazpeiner primært skyldtes erkendelsen af at de kan medføre alvorlig afhængighed og af nationale initiativer med henblik på at bremse forbruget og at den senere stigning i salg af SSRIere er en direkte konsekvens af markedføring, da effekten af SSRiere er overvurderet. Det andet studie viste at SSRI ophørssymptomer var meget tilsvarende benzodiazpine ophørssymptomer. Det giver derfor ikke mening kun at beskrive de sidstnævnte som afhængigheds-symptomer. Det tredje studie viste at i et forsigtighedsprincip perspektiv kan det opfattes som om lægemiddel myndighederhar afvist at erkende at SSRIere kan medføre afhængighed, med henvisning til diagnosemanualerne ICD-10 og DSM-IV og undervurderet problemet med hensyn til alvorlighed og hyppighed. I dette perspektiv er ændringer i kommunikationen om bivirkninger, fra lægemiddelmyndigheder til offentligheden, sket langsomt. I et risk management perspektiv kan det opfattes som om lægemiddel myndigheder har reageret i

overensstemmelse med den langsomt voksende viden om bivirkninger og har skærpet informationen til offentligheden over tid. Den spontane indberetning af bivirkninger lider under under-rapportering, hvilket er en væsentlig årsag til den langsomt voksende viden om bivirkninger.

4. Introduction

Psychotropic medicines have been available for physicians to prescribe since the middle of the 1800s. Although the active ingredients have changed over time, most of them have been associated with dependence (1,2). Barbiturates were introduced into the market in 1903 for treatment of insomnia and anxiety, but because of the risk of intoxication, dependence and misuse, the barbiturates were slowly replaced by the benzodiazepines, which have been available since the late 1950s (1,2). At the peak of their use, about 10% of the Danish population could have taken them on a daily basis (1), and they are still widely used, although the risk of dependence has been known since the beginning of the 1960s (1,3,4).

Before the 1950s, the general perception was that the transmission between the nerves was based on electric signals. During the 1950s and 1960s it became accepted that this transmission process was chemical and that it involved neurotransmitters like dopamine, norepinephrine, acetylcholine and serotonin. Modern psychotropic drugs developed from 1950 and onwards were believed to have more specific effects on the patient´s mood, thoughts and behaviour. This was the beginning of intensive research into molecular structures, receptors and the relation to specific disorders, which established connections between psychiatric aetiology, psychopharmacology and development and marketing of new psychiatric drugs (5).

In 1988, the so-called selective serotonin reuptake inhibitors (SSRIs) were introduced as new antidepressants and expectations were very high regarding efficacy and safety (2,4). The use of SSRIs rapidly increased in many countries and continued to increase during the next approximately 30 years without any peak or indication of a decrease (6).

Several studies have described increasing use of SSRIs and a decreasing use of benzodiazepines. A few studies have looked at overall usage (1,2) but most have focused on specific therapeutic drug groups (1,3,4,). Some international studies have described usage trends for antidepressants, all showing an increase from the beginning of the 1990s, due to the SSRIs, although in Australia, the

increase of SSRIs levelled out in the late 1990s (7). In the USA, the SSRIs have dominated the psychotropic market, while usage of benzodiazepines has declined (8). In Italy, there was a substantial increase in usage of antidepressants, especially the SSRIs, but in the same period usage (1995-2003) of benzodiazepines remained stable (9). Rose has described the development in prescribed SSRIs in the European countries, and the pattern was an increase in all countries (5). I describe in my thesis the total exposure of the Danish population to psychotropic drugs, with a focus on SSRIs and with benzodiazepines as comparator, and explore the possible reasons for the changes in usage.

Newer studies into SSRIs have contributed with evidence on efficacy. In 2010 J.C.Fournier et al (10) estimated the relative benefit of medication versus placebo in patients diagnosed with depression. The authors found that the magnitude of benefit of antidepressant medication increased with severity of depressive symptoms and that the effect was minimal or non-existent in patients with mild or moderate symptoms of depression.

The efficacy of SSRIs is much discussed in the literature. Studies have shown that the SSRIs are better than placebo in the treatment of depression (11)

Hans Melander et al (12) studied, and published also in 2003, the consequences of multiple publication, selective publication and selective reporting in studies of SSRIs sponsored by pharmaceutical companies. They found that it is not possible to recommend a specific SSRI from the publicly available data only, as the evidence is biased.

In 2008 Erick H. Turner et al (13) investigated how accurately the published literature conveyed data on drug efficacy to the practitioners, comparing the drug efficacy inferred from the published literature with the drug efficacy according to the US Food and Drug Administration (FDA) reviews on antidepressants. They found that there is selective publication of antidepressant studies, resulting in an increase in effect size ranging from 11 to 69% on individual drugs and 32% overall.

It is pretty clear that the inclusion of unpublished data seems to diminish the effect (12, 13). Kahn et al argue that treatment is effective for patients with severe depression but not for patients with mild to moderate depression (14). Thus, there is no consensus with respect to efficacy, which is expected, as so much has been left unpublished.

Peter Conrad has described medicalization as a process by which nonmedical problems become defined and treated as medical problems (15). According to Conrad the increase in medicalization could be explained not only by a medical colonisation of human life conditions but also a decreased tolerance to symptoms, social movements and patient organisations advocating for medicalization, pharmaceutical industry and disease mongering as a way to increase profit (15).

Joel Paris draws our attention to the problems of defining the boundaries of depression. "Depression is so prevalent that it has sometimes been called "the common cold of psychiatry" (16). But a cold should not be confused with pneumonia, even if both share some of the same pathological mechanisms. And treating colds as if they were pneumonia (i.e. with antibiotics) is just as mistaken as giving antidepressants to everyone whose mood is low" (16). But that is exactly the problem with depression that the DSM and ICD definitions are built on criteria which are difficult to distinguish from depressed feelings as a part of normal life. "It conflates normal unhappiness with the mental paralysis of melancholia". Paris also mentions the time criteria as a problem for over-diagnosing, as two weeks is a short time scale and is not evidence based. The same goes for the cutoff point of 5 out of 9 criteria that should be fulfilled for the diagnosis dependence. It is unclear where the 5 came from and whether it is a valid cutoff (16).

This is supported by Kendler and Gardner in a study from 1998 in which they found "little empirical support for the DSM-IV requirements for 2 week´ duration, five symptoms, or clinically significant impairment (17). These results suggest that major depression may be a diagnostic convention imposed on a continuum of depressive symptoms of varying severity and duration" (17). Also Roger Mulder describes that the differences between normal mood fluctuations and clinical depression are differences in degree but not kind (18). Diagnosing depression needs to move beyond the obvious symptoms but include the subject and the context, according to Mulder.

Benzodiazepines were recognised causing dependence during the 1980s. A few years after the launching of SSRIs, case studies began to be published describing withdrawal reactions and raising the question whether the SSRIs could cause dependence. Withdrawal reactions had already been described for the tricyclic antidepressants and the monoamine oxidase inhibitors (19).

A Danish study from 1995 showed a discrepancy between the use of antidepressants (all) in general practice and the scientifically-based recommendations with respect to treatment duration, indication, dose and therapy control. Further a number of patients stated that they had tried to stop medication, "but had failed to do so because they felt they could not do without it" and expressed feeling of being dependent on the treatment (20).

Ten years later most medical authorities do not regard antidepressants as causing dependence according to Peter Haddad (21).

For both the benzodiazepines and the SSRIs, discontinuation symptoms were in the beginning understood as relapse of the underlying illness because the symptoms are overlapping to some degree (22). During the 1990´s, the number of reports about SSRI discontinuation symptoms increased and this led to discussions whether discontinuation symptoms also represented dependence (23). The various views were reflected in the choice of terminology, so that authors believing that SSRIs could cause dependence preferred the term withdrawal syndrome and saw the term discontinuation symptoms as misleading.

In 1998, Haddad, Lejoyeux and Young suggested in an editorial in BMJ that the incidence of withdrawal reactions from SSRIs was 35%, mostly mild to moderate, short-lived, and preventable and simple to treat (24). This was reassessed by Young and Haddad in 2000 in a correspondence in The Lancet suggesting an incidence rate between 35% and 78% and with a characteristic SSRI withdrawal syndrome (25). Symptoms would normally be mild and transient, but could occasionally be of longer duration and cause considerable morbidity. The assessment was built on randomised controlled trials from 1995, 1997 and 1998.

In this perspective, we found it useful to explore the difference between benzodiazepine dependence and SSRI withdrawal syndrome.

The first two studies led to the third study about the drug authorities' reactions to benzodiazepine dependence and SSRI withdrawal syndrome and the way drug authorities informed the health professionals and the public about possible adverse reactions. It seems reasonable to explore how drug authorities informed the public about SSRI withdrawal reactions, as drug authorities have the responsibility to protect the public against adverse reactions. Joel Lexchin has written that, "Drug regulation would seem to be an easy task: make sure that the drugs that reach the public are safe and effective, and ensure that accurate information is provided about how to use these medications" (26). We raised several questions about drug regulation in our first two studies, but in the third, we focused on drug regulation and information about SSRI withdrawal and benzodiazepine dependence and on whether the information could be understood from a precautionary principle or a risk management principle, as described by Lexchin (26).

Drug agencies have the responsibility of protecting public health and have the authority to inform about drugs, both with respect to efficacy and to adverse effects. The information from drug agencies is important for patients, allowing them to make an informed choice, and for the decisions of prescribers. The society has an expectation that drug agencies will offer neutral and comprehensive information about drugs. Pharmacovigilance activities aim to protect public health (including regulatory action) and to communicate with and inform stakeholders and the public (27).

In this thesis one focus is on the use of SSRIs and the changes in use compared to benzodiazepines and in the light of the use of all psychotropic drugs. The other focus is on dependence or withdrawal reactions, which have been claimed by users of the drugs and rejected by the drug authorities and the manufacturers (21).

The suspicion of SSRI dependence was raised a few years after their marketing through the adverse-event reporting system. Nevertheless it has consistently been denied that the SSRIs could lead to dependence, both by marketing-holders, clinicians and authorities (28,29). When patients abruptly stop taking either benzodiazepines or SSRIs, the result is often a constellation of symptoms. However for benzodiazepines, this condition is labelled "dependence", but for SSRIs "withdrawal" reactions (28,29).

On the basis of literature and a document search for this thesis I created a timeline starting from the introduction of benzodiazepines in the late 1950s up till today (table 2) illustrating the medicines life-cycle.

4.1. List of abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
CPMP	Committee for Proprietary Medicinal Products (EMA)
CSM	Committee on Safety of Medicines
DDD	Defined daily dose. The assumed average dose per day for a medicinal product used for its main indication in adults.
DKMA	Danish Medicines Agency
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency (EU)
FDA	Food and Drug Administration (USA)
ICD	International Classification of Diseases
MAH	Marketing authorisation holder
MCA	Medicines Control Agency
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
N05	Nervous system: antipsychotics, anxiolytics, hypnotics and sedatives
N06	Nervous system: antidepressants, psychostimulants, psycholeptics and antidementia
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor

4.2. Overview of the project

Table 1

Sub-study aims	Methods	Results	Conclusions
Our primary aim was to compare the sales of SSRIs with that of benzodiazepines within the primary care sector in Denmark. We hypothesized that changes in sales of SSRIs were related to number of indications and number of products on the market.	Linking sales statistics over a period of four decades to indications and number of products.	There was an association between sales of SSRIs and the number of products on the market	Marketing pressure is a possible explanation for the increased sales of SSRIs.
To explore the possible rationale behind benzodiazepines being labelled as creating dependence and SSRIs not.	Documentary study and systematic literature review. Definitions over time of dependence and withdrawal reactions were analysed and related. The syndromes described for both medicine groups with regard to dependence and withdrawal reactions were compared.	The definition of substance dependence changed over time. Discontinuation symptoms are described with similar terms for benzodiazepines and SSRIs and are very similar for so-called SSRI withdrawal reactions and benzodiazepine dependence.	The withdrawal reactions to SSRIs were almost identical to those for benzodiazepines. It is therefore not rational to describe only the latter as dependence symptoms.
To explore the rationale behind benzodiazepines being accepted as addictive and SSRIs not. Indications of this are documents produced by prominent actors.	Documentary study. Documents with relation to either benzodiazepines or SSRIs were searched to construct a timetable for each drug group to explain the development in statements. We searched in pharmaceutical agencies for statements, announcements, initiatives, meeting minutes and other documents about SSRIs or the benzodiazepines.	It took its time to recognize benzodiazepine dependence and SSRI withdrawal reactions: more than 8 years to accept the frequency and seriousness of the dependence potential of benzodiazepines, based on two important papers from the Committee on Safety of Medicines (UK) from 1980 and 1988. It took 10 years	In the perspective of the precautionary principle it could be understood as if the drug agencies have refused to acknowledge that SSRIs can cause dependence, with reference to the diagnostic disease manuals ICD-10 and DSM-IV, and minimised the problem with regard to the severity and the number of people affected. In this perspective changes in the communication form

		to accept withdrawal reactions as a class effect of SSRIs and that withdrawal symptoms can be serious, based on an article from the Committee on Safety of Medicines in 1993 and the meeting minutes from the Committee in 2004.	drug regulators to the public about adverse effects happened slowly. In the perspective of the risk management principle it could be understood as if the drug agencies have reacted in concordance with the slow growing knowledge of adverse drug reactions and have sharpened the information to the public over time.

4.3. Timeline for benzodiazepine and SSRI

Table 2

Late 1950s	Benzodiazepines were launched in the late 1950´s
1961	Withdrawal reactions to imipramine (a tricyclic antidepressant) were described. A study about withdrawal reactions to benzodiazepines was published.
1962	
1963	
1964	Chlordiazepoxide was listed among substances especially liable to cause drug dependence.
1965	
1966	FDA noted that "these non-barbiturates sedative drugs [benzodiazepines] can cause states of intoxication and physical dependence that are clinically similar to those introduced by barbiturates".
1967	Warnings that benzodiazepines were used illicitly.
1968	
1969	
1970	
1971	
1972	
1973	
1974	
1975	
1976	
1977	
1978	
1979	The labelling of benzodiazepines was changed to include a note that long-tern use had not been systematically studied. A US Congress hearing about the "Valium scare" took place. Benzodiazepines were afterwards categorised as having both medical and abuse potentials and included as so-called Schedule IV drugs according to the UN Controlled Substances Act of 1970.
1980	The Diagnostic Statistics Manual of Mental Disorders (DSM-III) was published by the American Psychiatric Association. The dependence potential of benzodiazepines was recognised by the UK authorities but as rare, and limited use of benzodiazepines was recommended due to absence of long-term efficacy and safety data.
1981	
1982	
1983	
1984	More benzodiazepines were categorised as having abuse potentials and therefore included in the Schedule IV of the 1971 United Nations Convention on Psychotropic Substances.
1985	
1986	
1987	DSM-IIIR published. The definition of dependence was changed and several more criteria

	than in the former DSM-III were described.
1988	The first SSRIs were launched. Committee on Safety of Medicines (UK) published a new statement that benzodiazepines cause dependence. It was recommended to use the drugs only for two to four weeks. The Committee concluded that dependence to benzodiazepines was "becoming increasingly worrying".
1989	
1990	
1991	Case reports about SSRI withdrawal reactions published
1992	The International Classification of Diseases (ICD-10) was published. Withdrawal reactions were described as an autonomous diagnosis at the same level as dependence.
1993	MCA (UK) published a warning to prescribers and patients about the possibility of withdrawal reactions from paroxetine, based on spontaneous reporting.
1994	DSM-IV published. Withdrawal reactions were described as an autonomous diagnosis at the same level as dependence.
1995	Flunitrazepam was transferred from Schedule IV to the more restrictive Schedule III in the 1971 United Nations Convention on Psychotropic Substances.
1996	Authorities describe SSRI withdrawal reactions as rare and relatively mild. Closed symposium on "Antidepressant discontinuation events" sponsored by Eli Lilly. UK authorities published a review of SSRI withdrawal reactions with the conclusion that there was no evidence of a physical dependence problem with the SSRIs and that withdrawal reactions were rare and "relatively mild".
1997	A supplement to the Journal of Clinical Psychiatry was published with several proceedings from the symposium in 1996. The supplement was sponsored by Eli Lilly.
1998	At a meeting in the Committee on Safety of Medicines (UK) an Eli Lilly representative expressed concern of the use of the term "withdrawal reaction" when referring to the symptoms occurring on withdrawing treatment due to the fact that the term "withdrawal" has a specific meaning and implies that the drug is addictive. Lilly suggested the term "discontinuation reactions". Charles Medawar likened SSRIs to benzodiazepines with respect to their ability to cause dependence, which started a review process in EMA (Europe) and in MCA (UK). It was suggested in an editorial in BMJ that the incidence of withdrawal reactions from SSRIs was 35%, mostly mild to moderate, shortlived, preventable and simple to treat.
1999	
2000	Committee for Proprietay Medicinal Products: "the studies were not designed to study withdrawal phenomena in SSRIs. It was suggested in a correspondence in The Lancet that there was an incidence rate of withdrawal reactions between 35% and 78% and with a characteristic SSRI withdrawal syndrome.
2001	
2002	SSRIs were among the 30 highest-ranking drugs in the list of drugs for which dependence has ever been reported to the Uppsala Monitoring Centre database. In USA paroxetine had been marketed directly to consumers as "non-habit forming" but FDA published a warning against paroxetine and the risk of withdrawal symptoms.
2003	Data on the frequency of withdrawal reactions after use of paroxetine were presented at a meeting in the Committee on Safety of Medicines: 10% of the patients may experience withdrawal reactions due to paroxetine.

2004	Expert working group on the safety of SSRIs published a report with the main conclusion that there was no clear evidence that SSRIs have a significant dependence liability or showed development of a dependence syndrome, with reference to DSM-IV and ICD-10. SSRIs met three out of seven DSM IV criteria, but the extent to which these criteria were met was assessed to be much smaller than for other typically dependence-producing drugs and the data revealed no evidence that these drugs are associated with dependence.
2005	
2006	Financial ties between DSM-IV panel members and the pharmaceutical industry were revealed.
2007	
2008	Around 100,000 Danes out of a population of 5.5 million people were in long-term treatment with benzodiazepines.
2009	
2010	

5. Objectives

In the light of this the following objectives of the PhD project were defined:

- to compare the sales of SSRIs with that of benzodiazepines within the primary care sector in Denmark. We hypothesized that changes in sales of SSRIs were related to number of indications and number of products on the market.
- to explore the possible rationale behind that benzodiazepines are accepted as producing dependence and SSRIs are not.
- to explore how changes in the adverse reaction profiles of benzodiazepines and SSRIs with respect to dependence and withdrawal reactions were reflected in the communication from medicines agencies and other relevant health authorities to the public over time.

6. Methods, results and discussion

The study was organised according to the three specific objectives which appear from page 22. Study 1 was based on sales statistics, primarily from the Danish Medicines Agency but also from other sources. The second study was based on the diagnostic manuals on psychiatric disorders (DSM III, IIIR, IV) (30-32) the international classification of diseases (ICD-10) (33) and a systematic literature search on PubMed. The third study was performed as a documentary study. I will discuss the materials, methods and results in the following.

Paper 1

Title: An analysis of psychotropic drug sales. Increasing sales of selective serotonin reuptake inhibitors are closely related to number of products.

In this study, we explored the sales statistics of all psychotropic drugs in Denmark, with a focus on benzodiazepines and SSRIs. It was expected that the sales pattern of SSRIs and benzodiazepines would be much alike (until the decrease in sales of benzodiazepines began) and that these sales patterns could be understood with the same explanations, e.g. number of indications and number of products.We also explored the changes in indications for the two drug groups and the number of products on the market.

We looked at all psychotropic drugs and the changes in sales pattern. This can be discussed, because they are very different drugs, e.g. antidementia drugs, antidepressants and hypnotics. This gave us, however, an overview of the changes in sales patterns including treatment changes between classes of drugs, e.g. between benzodiazepines and SSRIs, which together represented the main part of the sales of psychotropic drugs. The full data set was used as background data for the description in development in sales of SSRIs and benzodiazepines.

The efficacy of SSRIs may not be able to explain the increase in use, as there is no consensus with respect to efficacy of SSRIs (10, 11), which is why other explanations were explored. A Danish study has shown that general practitioners receive a median of 19 visits from drug representatives during six months and that the drug industry uses a variety of methods to get their message across

including gifts, drug samples and invitations to courses and meetings (34). A Swedish study showed that psychiatrists found the information given by the pharmaceutical industry as the most important information about SSRIs (35). Furthermore, disease awareness campaigns with patients, or citizens who feel they are healthy, as the target group have been instituted. This offers support to the hypothesis that the increasing sales could be related to the number of indications and number of products on the market and thus to marketing initiatives.

Method

Data about sales were derived from four different data sources, which were combined in order to create sales statistics over a long period of time. One source, presenting the oldest data, was a Danish study of sales of psychotropic drugs building on data from Danish Drug Statistics. The data included in Hansen and Gyldmark (1990) were older than the ATC-system, but the way data was classified was very close to the ATC-system, and could therefore, with a few exceptions which Hansen and Gyldmark have clarified, be imported into the ATC-system (1). The second source was also Danish Drug Statistics, but directly as primary source. The third source was Danish Medicines Information, because the sales statistics for two years, 1992 and 1993, have never been published, but were available on request. The last and fourth source was The Danish Medicines Agency, which from 1994 has been responsible for the sales statistics in Denmark publishing these annually. There was consistency between the data sources and there were overlaps between sales data between the different sources, which confirmed the consistency.

Table 3: Data description

Source	Produced by	Date, period	Data	Measurement
Hansen and Gyldmark	Danish Drug Statistics	1970–1981	Wholesalers	ATC, DDD
Danish Drug Statistics	Danish Drug Statistics	1981–1991	Wholesalers	ATC, DDD
Danish Medicines Information	Danish Medicines Information	1992 and 1993	Wholesalers	ATC, DDD

(DLI)				
The Danish Medicines Agency	The Danish Medicines Agency	1994–2007	Pharmacy dispensing	ATC, DDD

In 1993 it was decided to establish the Register of Medicinal Products Statistics, because of a political wish of a publicly run register, which could strengthen health authorities´ decision foundation. The Danish Medicines Agency owns and is responsible for the register. On a global scale, the register is unique as it is the only register about consumption (sales), covering the entire population of a country over many years. Around 30 different variables are registered in relation to sales of drugs on prescription in primary health care. The following data were used: Anatomical Therapeutic Chemical Classification (ATC-code) and defined daily doses (DDDs). The ATC system is described in a very short form in the paper. A more thorough description is that drugs are classified in groups at five different levels. The drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups (36). The basic definition of DDD is that DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (36). According to the WHO Collaboration Center for Drug Statistics Methodology, drug consumption figures should preferably be presented as numbers of DDDs/1000 inhabitants/day.

The study focused on the primary health care sector in Denmark. One reason for this was that the main part (80-90%) of the sales of psychotropic drugs was and still is prescribed in the primary health care sector by general practitioners (37) and as the vast majority of patients treated for a mental condition are treated in general practice (38). We estimated that the secondary health sector contributed with only a small part of the total sale and that exclusion of these numbers could not change the overall picture of sales. Another reason was that it was not possible to get data for sales in the secondary health care sector for the whole period, so this could have limited the period of study.

The data in the register represent sales and prescribing data but they cannot be taken as equivalent to taken drugs. Some of the prescribed and sold drugs will never be taken as prescribed and there is little knowledge about what happens to the drugs after purchase in a pharmacy. All purchases of prescribed drugs in a pharmacy are included in the register. There might be a minor proportion of drugs offered in outpatient clinics or by general practitioners, as free samples are given by drug companies, resulting in under-reporting. Given these considerations, there is no reason to assume that the Register of Medicinal Product Statistics should not be valid.

Data about products and indications were obtained from the Danish Drug Index, which has been published yearly in the whole period. Danish Drug Information, owned by The Danish Association of the Pharmaceutical Industry, has published the Danish Drug Index.

We performed a correlation coefficient analysis of the association between DDD sales numbers and number of products well knowing that it is not possible to conclude about causation. Thus the study can make it plausible that there is an association between the sales and marketing.

We looked at all psychotropic drugs and the changes in sales pattern. This could be discussed, because they are very different drugs, e.g. antidementia drugs, antidepressants and hypnotics. This gave though an overview of the changes in sales patterns including treatment changes between drugs, e.g. between benzodiazepines and SSRIs, which together represented the main part of the sales of psychotropic drugs.

By means of a combination of three data sets of the sales of psychotropic drugs it was possible to construct sales curve of psychotropic drugs in Denmark in the primary health care sector over a 37 years period.

Results

The sales of psychotropic drugs have fluctuated considerably over time even though the prevalence of the diseases should be expected to be about the same (figure 1). When the total sales of psychotropics were split into drug groups, sales of group N05, which contains the benzodiazepines,

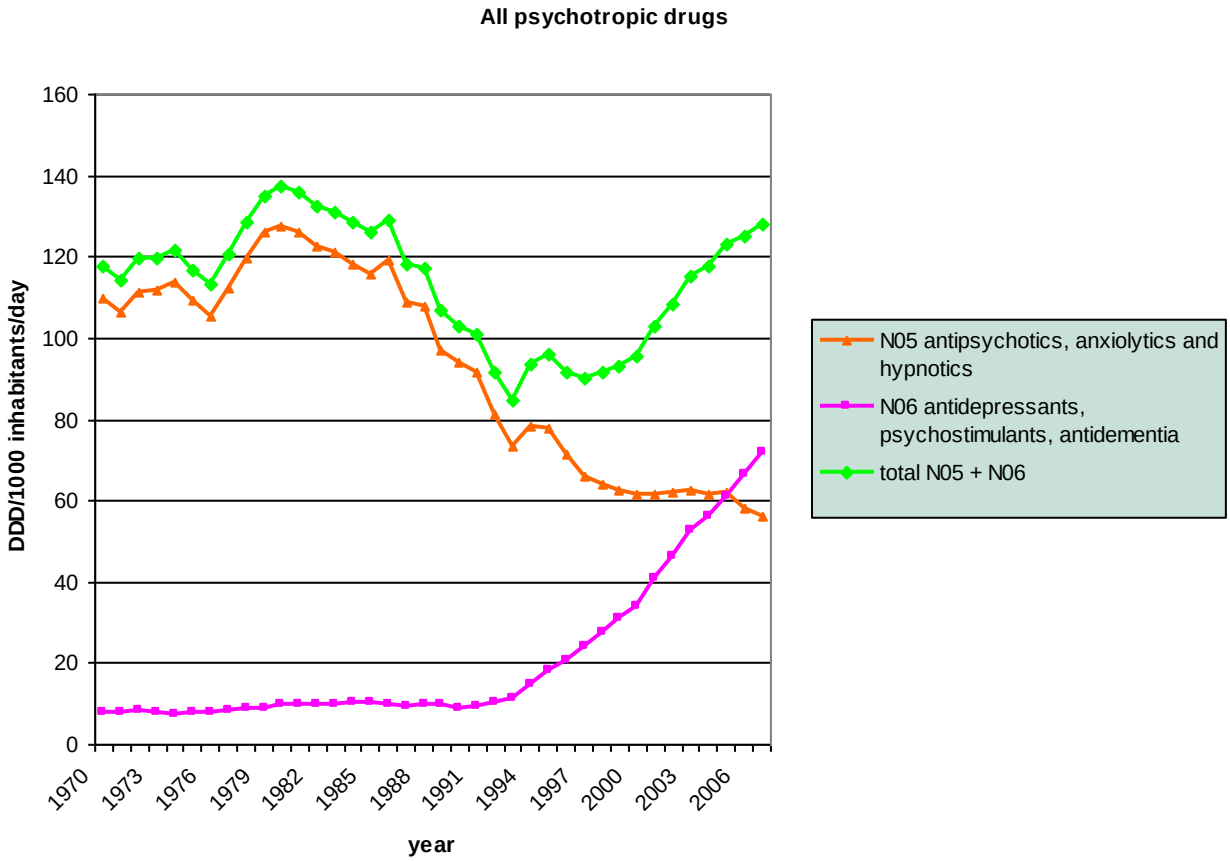
increased until 1986 and thereafter decreased. As benzodiazepines are the biggest drug group (in number of DDDs) in N05, they are mainly responsible for the trend.

The number of products on the market increased up to 1996 and peaked with 48 benzodiazepine products and thereafter decreased. The number of indications increased from 8 in 1983 to 11 in 2005. So while the sales decreased from 1986, the number of products on the market continued to increase for 10 more years and then started to decrease. The number of indications has continued to increase.

The sales of group N06, which contains all antidepressants, from 1988 also the SSRIs, was steady and low for the first 20 years. After this period the curve increases linearly. The SSRIs are the biggest drug group in number of DDDs in N06 and are thus mainly responsible for the trend.

From 1992 to 2007, DDD for the SSRIs increased from 2.5 to 43.9, i.e. by a factor of 18. A closely similar increase was seen in the number of different SSRI products on the Danish market, including brands and generics, which increased in the same period from 3 to 47, i.e. by a factor of 16 ($r = 0.97$ for the correlation). Twenty-three different drug companies marketed the 47 different products in Denmark in 2007. The number of indications for treatment with SSRIs increased from 1 in 1992 to 8 in 2008.

Figure 1: Sales of all psychotropic drugs in DDDs in the period 1970 to 2007



The most likely explanation for the decline in sales of benzodiazepines is the recognition that they cause serious dependence which started initiatives at a national level to curb their use, and the recent steep increase in sales of SSRIs is likely a direct consequence of marketing pressures.

The increase in sales of SSRIs could also be influenced by an increase in the prevalence of mental disorders, but Kessler et al (39) showed that the prevalence of mental disorders did not change in the United States (1980-1992 and 2001-2003). They concluded that despite the increase in the rate of treatment, most patients with a mental disorder did not receive treatment and half of those who did receive treatment did not have a mental disorder meeting the diagnostic criteria. Therefore it seems reasonable to discuss whether the increased rate of treatment may have been due to aggressive direct-to-consumer marketing of new psychotropic medicines in USA. Direct-to-consumer advertisement is not legal in Europe, but instead disease awareness campaigns have been

used (29). The study by Kessler et al supports our conclusion that explanations of increased sales of SSRIs should not be found in increased prevalence but in other factors such as marketing (39).

The results find support in a Swedish study from 1994. It was a survey directed to Swedish psychiatrists, trying to find explanations of the increased usage of SSRIs. The psychiatrists found that the information given by the pharmaceutical industry was the most important information about SSRIs (35). There is reason to believe that general practitioners, who are also the target group for very active marketing, have the same perception of the information from the industry (40). Another result from the Swedish study was that the psychiatrists mentioned 13 indications for SSRI treatment, while only two indications were approved at that time, which can be understood as an indication slide even though doctors have a free prescription right.

A Norwegian survey from 2004 showed that almost half of the doctors found that they were not influenced by contact to the drug industry and that the relation between doctor and the industry was subjected to too much control from the society (41).

Pirraglia et al. have shown that the prevalence of antidepressant use in adult primary care has risen dramatically since 1989, reflecting use of new agents (42). Further, they have shown that the pattern of increased use is remarkable, with each new and potentially competitive agent adding to aggregate use without concomitant decrease in previously introduced newer agents. The authors explain that this is likely to reflect, in part, aggressive marketing by pharmaceutical companies.

A study by De Las Cuevas et al. also supports the conclusion that marketing plays an important role in prescription rates (43). They have shown a remarkable variation in antidepressant prescription by psychiatrists and general practitioners, which are explained among other factors by marketing pressure. “The present extent of physician–industry interactions appears to affect prescribing and professional behaviour and should be further addressed at the level of policy and education.”(43).

The prevalence of major depressive episodes varied according to the International Consortium of Psychiatric Epidemiology (44) study from 3% in Japan to 16.9% in US, but most lifetime prevalences were in the range 8-12% (all severities) (44).

Under- and overdiagnosing have often been brought into the debate about depression and the increased treatment rate with SSRIs. Mitchell et al expressed it this way in a meta-analysis: “In

general, a motivated GP in an urban setting (where the rate of depression is 20%) would correctly diagnose ten out of 20 cases, missing ten true positives. The GP would correctly reassure 65 out of 80 non-depressed individuals, falsely diagnosing 15 people as depressed" (45). Thus there is both an under- and an over-diagnosing problem, and according to Mitchell´s conclusion false positives contribute considerably to the increased treatment rate (45).

It is plausible that some of the psychotropic treatment has been changed from the benzodiazepines to the SSRIs, as some of the indications are the same. There is, however no evidence for this. A study by Berney et al (46) concluded that the change of the prescribing pattern from benzodiazepines to newer antidepressants was not based on evidence with a high level of proof, since there is only one double-blind, randomized controlled trial comparing one of these antidepressants to a benzodiazepine, among 274 double-blind, randomized trials on drug efficacy in panic disorder, generalized anxiety, social phobia and post-traumatic stress disorder.

Discussion

Two books have been published in 2010, both of them trying to explain or understand why diagnosed depression has increased so rapidly over the last 60 years. In the first book Alain Ehrenberg (47) sees a depression epidemic in the modern society as a real phenomenon. The individual in the modern society shall perform and unfold itself and this demand of self-realisation is followed by a responsibility for the individual´s own success and happiness. The good message, according to Ehrenberg, is that doctors today are able to offer a diagnosis and a treatment, antidepressants, and the modern human being can get relief, when unable to fulfil the demands of success and happiness.

In the second book Gary Greenberg (48) offers another explanation of the epidemic of depression. The introduction of the new antidepressants, SSRI, with fewer adverse effects than the older antidepressants, played together with the new diagnostic tools in the DSM-IV, with which general practitioners were able to diagnose more patients as depressive than before. Also the way people were talking about depression changed, because of a new theory that depression was caused by a biochemical imbalance in the brain with lack of serotonine, which could be cured with the new

antidepressants. This theory is not evidence based, but has, according to Greenberg, great impact on our current perceptions of depression and its treatment.

Abraham (49) has described pharmaceuticalization as a new term, covering something else than medicalization. Medicalization is when normal life events, like depressed mood or anxiety before making a speech in front of an audience, is changed to a pathological event with a diagnosis and a treatment. Pharmaceuticalization is an increasing use of pharmaceuticals, not only in the case of medicalization but that pharmaceuticals are always the first choice of treatment and are used without balancing the harms and benefits. This also offers an explanation of the increased rate of treatment that seems to have affected both professionals and lay people.

Paper 2

Title: What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin reuptake inhibitors.

In this study, we aimed at exploring the rationale behind benzodiazepines conceived as being addictive and SSRIs not, but causing withdrawal reactions and a withdrawal syndrome.

Methods

It was a literature review, involving a description and analysis of the diagnostic manuals DSM-III (1980) (30), DSM-IIIR (1987) (31), DSM-IV(1994) (32) and ICD-10 (1992) (33) concerning the definition of dependence and the changes in definition over time. The diagnosis withdrawal syndrome is only described in DSM-IV and in ICD-10, where it was made an autonomous diagnosis at the same level as dependence, and at the same time one of several criteria for the diagnosis dependence. The DSM-IV sourcebook (50) contained the documentation behind the DSM-IV and its definition of dependence, and it raises some problems and discussions from the DSM working group about the definition of drug dependence, which is mostly based on knowledge and evidence about other substances than prescription drugs, mainly alcohol, opium and heroin.

The DSM is organized around working groups or panels, e.g. mood disorders group. The American Psychiatric Association (APA) has published DSM since 1952 (50). The International Classification

of Diseases (ICD) is organized by the WHO and has a structure of topic related working groups and an advisory board. The diagnostic manuals form the basis for health statistics, health expenditure, monitoring and research. There has been a harmonisation process between DSM-IV and ICD-10, but there are still some differences between the two. We have analysed the documents as public, professional and internationally accepted diagnostic manuals, which influence the diagnoses involved in our study.

The other part of data in our study is from a PubMed literature search on studies describing dependence and withdrawal symptoms from benzodiazepines and SSRIs. The search strategy is described in the article. We excluded case studies, because they are numerous and because many of the included studies have included case studies. We might not have caught all studies describing dependence or withdrawal symptoms, but we have found enough, as there seems to be a high degree of accordance between them and as many symptoms are described in several studies and some symptoms are described in almost all studies. Although we performed a thorough literature search, including scrutinizing reference lists in identified papers, literature searches always have limitations, e.g. due to limitations in databases, limitations in search terms and access to documents. Hence, we cannot preclude that we have missed relevant references.

In order to analyse the identified withdrawal symptoms, we had to systematize them and we adopted a categorisation, which has previously been used for antidepressant discontinuation symptoms (51,52). The process is presented in the article.

We have not included frequency and severity of the symptoms, which could have enlightened differences, if any, in the characteristics of benzodiazepine dependence contra SSRI withdrawal syndrome. The study focuses on whether there is reasonable agreement between benzodiazepine dependence symptoms and SSRI withdrawal symptoms.

Results

The bar for the diagnosis dependence was raised in 1987 with DSM-IIIR, just before the SSRIs were launched. The change implied that more criteria, including behavioural, physiological and cognitive manifestations and a time criterion had to be fulfilled for the diagnosis of dependence (table 4). The scientific documentation behind this change is mainly built on knowledge about

alcohol and opiates (50). The withdrawal syndrome was launched as an autonomous diagnosis but also one of the criteria for dependence in DSM-IV. We identified a range of symptoms (table 5), many of them described in several ways, using various words. We also found that the withdrawal reactions to SSRIs were very similar to those for benzodiazepines. It therefore makes no sense in rational pharmacotherapy to describe only the latter as dependence symptoms and it seems more semantic than evidence based to diagnose two similar symptom patterns with two different diagnoses.

Table 4: Definition of dependence in DSM and ICD:

Definition of dependence in the classification systems DSM and ICD			
	Manifestation criteria	Time criteria	Number of manifestations required
DSM-III (1980)	Tolerance to the substance or withdrawal symptoms.	No time criteria.	1
DSM-IIIR (1987)	Tolerance, withdrawal symptoms, much time spent to get the drug, not able to cut down use, uncontrolled use, continued use despite problems, normal activities are given up, the drug relieves withdrawal symptoms,	One month or manifestations have occurred repeatedly over a longer period.	At least 3 of the manifestations.
ICD-10 (1992)	Tolerance, withdrawal symptoms, preoccupation with drug use, compulsion to take the drug, uncontrolled use, persistent use despite problems.	One month or if less than a month then manifestations should have occurred together repeatedly within a 12 month period.	3 or more of the manifestations.
DSM-IV (1994)	Tolerance, withdrawal symptoms, much time spent to get the drug, not able to cut down use, uncontrolled use, continued use despite problems, normal activities are given up.	Manifestations occur at any time in the same 12-month period.	3 or more of the manifestations.

Table 5: A comparison of benzodiazepine dependence symptoms and SSRI withdrawal symptoms as described in the literature:

Benzodiazepines	SSRIs
influenza-like symptoms	flu-like symptoms
diaphoresis, sweating, flushing	sweating
headache	headache
fits, convulsions, seizure	convulsions
muscle aches, muscular pains	myalgias
fatigue, lack of energy, lethargy	lethargy, fatigue, somnolence
stiffness	arthralgias

palpitations	
skin rash, itching	
abdominal pain, abdominal cramps	abdominal cramping, abdominal pain
nausea, vomiting, dry retchings	nausea, vomiting
loss of appetite, weight loss, anorexia	appetite disturbance, anorexia
diarrhoea, constipation	diarrhoea
sleep disturbance	sleep disturbance
nightmares	nightmares, vivid dreaming
ataxia	ataxia
dizziness	dizziness
lightheadedness	lightheadedness
vertigo	vertigo
blurrred vision, difficulty in focusing	blurrred vision, visual disturbance
sore eyes	sore eyes
feeling of electric shocks, pins and needles	electric shock sensations
numbness	numbness
parasthesia, muscle twitches, tingling, altered sensation, fasciculation	parasthesia, restless legs, tingling
increased acuity to sound, smell, touch, pain, tinnitus, hyperosmia, photophobia, hyperaccusis	tinnitus, rushing noise in head
altered taste, metallic taste in mouth,	taste perversion
jerks, myoclonic jerks, jumpiness	myoclonic jerks
tremor, tremulousness, shakiness	tremor, shaking
incoordination, impaired perception of movement	imbalance, unsteady gait
	parkinsonism
agitation	agitation
aggression	aggression, anger
irritability, restlessness	irritability
mental tension	feeling tense
anxiety, panic attacks, agoraphobia, dysphoria	anxiety, sudden panic

depressed mood, depression	low mood, emotional lability, depression
nervousness	nervousness
depersonalisation	depersonalisation
derealisation, perceptual disturbance, paranoid reaction, delirium	detachment
confusion	confusion
poor concentration	decreased concentration, slowed thinking
poor memory	memory problems, amnesia
	bouts of crying
hallucination	hallucination
delirium	delirium
psychosis	catatonia

Discussion

"Most medical authorities do not regard antidepressants as causing dependence, or addiction, but this view has been challenged on the basis that these drugs can cause withdrawal symptoms and that in some patients these symptoms prevent antidepressants being stopped". This was the introduction to an article by Peter Haddad in 2005 (21). While case reports for withdrawal symptoms to SSRIs began to be published in the 1990´s, it was at the same time deliberately tried to change the terminology from withdrawal syndrome to discontinuation syndrome, in order to distance the syndrome from dependence, as lay people associated withdrawal with dependence. Eli Lilly took the initiative to arrange a panel of opinion leaders to discuss the terminology of discontinuation and withdrawal syndrome. Eli Lilly also brought up the discussion of terminology in the UK medicines agency, but without being supported. (52).

Many authors deliberately use the term discontinuation symptoms in order to distance the disorder to a withdrawal syndrome and dependence and as a euphemism instead of withdrawal syndrome, of

which withdrawal reaction is one criterion. (23, 52-55)

For antidepressants, withdrawal reactions were first reported with imipramine, a tricyclic antidepressant (TCA), in 1959 and were described in detail in 1961 by Kramer, Klein and Fink (56). The conclusion was that "The withdrawal syndrome complicates the evaluation of patients after drug discontinuation since both patients and physicians often interpret the onset of symptoms as an upsurge of "anxiety" related to incipient relapse, and resume treatment with the gratifying subsidence of the "anxiety". This may cause both patients and physicians to overvalue the importance of the medication to the patient´s stability".

In 1971 Oswald et al. (57) published an article with the conclusion that certain mood-influencing drugs may not be drugs of abuse, because of some unpleasant adverse effects, but that they can nevertheless be drugs of dependence. Both articles contributed to the development of the concept of therapeutic drug dependence and normal dose dependence. However, SSRI withdrawal syndrome is still mainly described on the basis of knowledge about opiate and alcohol withdrawal. The therapeutic drug dependence concept has not been included into of the dependence criteria and is not mentioned in the DSM-IV source book (50).

Patients should be fully informed in order to be able to assess benefits and harms before accepting a treatment and in accordance with the principles for informed choice. Further, it is important for patients to have their adverse effects accepted at face value. As many people find it difficult to discontinue treatment with SSRIs because of symptoms, the general perception is dependence.

There are different levels of epistemology with respect to withdrawal syndrome and dependence. Withdrawal symptoms are observable substance specific symptoms caused by discontinuation or reduction in substance use, causing physical and psychological distress. In contradiction hereto, dependence is based on a number of criteria that do not present themselves as symptoms but as behavioural aspects and a compulsive pattern of drug use as premises for the diagnosis. The dependence criteria are not observable in the same way as withdrawal reactions. Further, DSM diagnoses are the result of negotiations and consensus between experts and in that way, they are social constructs, which are rarely evidence based (58).

Paper 3.

Title: Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did the health authorities react?

In this study, we followed up on study 2 exploring why benzodiazepines are called addictive while SSRIs are said to cause withdrawal symptoms. The objective of this study was to explore the communications from drug agencies to the public about benzodiazepine dependence and SSRI withdrawal reactions over time, as the risk profile of the drugs changed over time. The communications from drug agencies might reflect the rationale behind the distinction between the drugs´ adverse effects.

Methods

The approach was an analysis of documents because this is a possible way of enlightening a historic course (59), with focus on the regulatory authorities and their statements about benzodiazepine dependence and SSRI withdrawal reactions. Documents in this case were official and publicly available as meeting minutes, articles from professional journals, official and published statements and they can express a rationale at the moment when the document was written. The sender of the document, in this case drug agencies, could expect that the documents at any time could be an object for subsequent study and analysis. On the other hand, we, as researchers, analyse in a certain time context and we also know the history. This might bias the analyses. The analysis of the documents focused on three document characteristics: the context of the document, the process or interactions that the document was part of and the facts that the document was a carrier of. The rationale behind this kind of research method is that documents "do" something as soon as they are written. The documents are written in the context of a drug agency (Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, European Medicines Agency, Danish Medicines Agency), representing an authority with the responsibility for an official and professional assessment of drugs. The documents get a status by the context they are written in. Many of the documents we have identified in this study are relating to each other.

It was not possible to use a systematic search strategy, which is in accordance with the document analysis approach, as a qualitative research method. We have, apart from a general search strategy described in the paper as figure 1, used a snowball method, by which references between documents are used to identify further documents to include into the analysis.

In the analysis of the documents the focus was on the institutional context, the genre of the document and the content. All the documents are given validity through their publication from a public authority. With the publication of a document the authority is defining the reality and if the definition should be challenged this would also challenge the authority.

This study is based on a not systematic document search in the drug authorities´ positioning with regard to benzodiazepine dependence and SSRI withdrawal syndrome. It was not a possibility to perform a systematic search and this is a limitation of this study. There might exist documents that it was not possible to search or that the search strategy did not catch up.

Results

We identified 6 documents for the benzodiazepines and 23 documents for the SSRIs (table 1). All documents are official and convey drug regulators' positions, express one-way communication and are authoritative. Public focus on SSRI withdrawal syndrome initiated a review process, during which working groups were established in drug agencies, referring to each other in the documents.

Table 1

Description of the documents included in the study:

Benzodiazepines

Year	Reference	Citation	Genre
1964	BMJ 1964, 31. October Drugs of addiction	List of substances especial liable to cause drug-dependence: Librium, chlordiaze-poxide	Article in BMJ.
1980	Committee on the Review of Medicines (1980). Systematic review of benzodiazepines. BMJ;280, 910-2.	However, following an extensive review of all available data the committee concluded that, on the present available evidence, the true addiction potential of benzodiazepines was low. The number dependent on benzodiazepines in the UK from 1960 to 1977 has been estimated to be 28 persons.	Systematic review
1980	Cirkulære om lægers ordination af afhængighedsskabende lægemidler [Circular	[All mentioned groups of drugs can cause addiction. The risk is greatest for morphine and	Circular – a law text

	about doctors prescriptions of addictive medicines]. Circular number 97 15.06.1980 Danish National Board of Health	amphetamine. The doctor shall, when prescribing anxiolytics or hypnotics, take care that the patient only is prescribed what seems reasonable for the treatment.]	
1980 - 1982	Medical Research Council Headquarters file 1980-82 http://www.benzo.org.uk/amisc/mrc82.pdf	Professor Lader explained that he thought that there was a "iceberg effect" of benzodiazepine dependence. A pronounced withdrawal syndrome showed up as a consistent pattern of physiological changes on withdrawal of the drug. Although dependence occurs in only a small proportion of benzodiazepine takers the number of patients involved may be substantial. The risks of dependence could be reduced by more trained prescribing of benzodiazepine.	Headquarters file, with letter, minutes, notes. Name of file: Benzodiazepine dependence.
1988	Medicines Control Agency, Committee on Safety of Medicines (1988). Benzodiazepines, dependence and withdrawal symptoms. Current problems in Pharmacovigilance, 21, 1-2.	There has been concern for many years regarding benzodiazpine dependence (Br.Med.J,1980:280:910-12). Such dependence is becoming increasingly worrying.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners.
1993	Circular about prescription of addictive drugs. Circular number 110 28/06/1993. Danish National Board of Health.	[Usage in Denmark is above the international average. It is not the intension with these guidelines to question current treatment. They are for short term treatment. For severe, disabling cases.]	Circular – a law text

SSRIs

Year	Reference	Citation	Genre
1993	Medicines Control Agency, Committee on Safety of Medicines (1993). Dystonia and withdrawal symptoms with paroxetine (Seroxat). Current problems in pharmacovigilance 19, February.	We have received 78 reports of symptoms occurring on withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion. Such reactions have been reported more often with paroxetine than with other SSRIs.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners
1996	Price J.S, Waller P.C., Wood S.M, Mackay A.V.P. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. British Journal Clinical Pharmacology. 1996;42:757-63.	It appears that the reports represent genuine withdrawal reactions, but the low frequency of reporting per thousand prescriptions, together with the published comparative studies suggest that, overall symptoms due to stopping an SSRI are rare. The withdrawal symptoms observed do not appear to be severe.	Scientific paper
1998	Committee on Safety of Medicines subcommittee on pharmacovigilance	However, withdrawal reactions occur with all SSRIs and related antidepressants, although to different extents with each drug, and this is now thought to be a class effect. In the main, these reactions are mild and self-limiting, although more severe reactions have been reported	Minutes
1998	Committee on Safety of Medicines. Summary of the meeting of the Committee on Safety of Medicines Held on Thursday 26 March 1998.	They [the committee] commented that dose escalation and drug seeking behaviour were evident in	Minutes

	http://www.mhra.gov.uk/home/groups/l-cs-el/documents/committeedocument/con003341.pdf	association with benzodiazepines but that these features were not evident in patients taking SSRIs.	
2000	European Medicines Agency (1999/2000). EMEA/CPMP/2775/99.	The material provided by the pharmaceutical companies with regard to dependence and withdrawal of SSRIs is of variable quality and quantity. For the majority of the compounds the studies were not designed to study withdrawal phenomena and lack sufficient observations in the critical period after stopping administration.	Position paper
2000	Medicines Control Agency, Committee on Safety of Medicines (2000). Current problems in pharmacovigilance,	In 1993 we alerted prescribers to the possibility of withdrawal reactions occurring with paroxetine. Whilst the withdrawal symptoms reported were generally not serious, there have been isolated reports of more serious symptoms on withdrawal such as severe electric shock sensations, vertigo and manic reactions.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners
2000	EMEA CPMP 2278/00	Some of the SSRIs have been shown to reduce intake of addictive substances like cocaine and ethanol. The interpretation of this aspect is difficult.	
2002	Tonks A. (2002). Withdrawal from paroxetine can be severe, warns FDA. British Medical Journal, 324, 260.	FDA Warning against paroxetine because of the risk of withdrawal symptoms.	News in BMJ
2002	MHRA response to Panorama programme on Seroxat	All SSRIs may be associated with withdrawal reactions on stopping but they are not drugs of dependence.	Safety message
2002	Ad Hoc Expert Meeting 21 November on the safety of SSRIs	The Group did not consider that withdrawal reactions and dependence were synonymous. The Group did not consider that SSRIs caused dependence.	Minutes
2003	DKMA Danish Medicines Agency (19 June 2003). Summary of Product Characteristics for Serorex (paroxetine) http://www.produktresume.dk/docushare/dsweb/Get/Document-14813/Serorex%2C+filmovertrukne+tabletter+20+mg.doc	[Though abstinence reactions can occur at discontinuation, all preclinical and clinical data do not indicate that SSRIs cause dependence]	SPC
2003	DKMA Lægemiddelstyrelsen (2003). Antidepressive midler under vurdering (Antidepressants under assessment).	[It is important to emphasize that it is about discontinuation symptoms and not actual dependence to the drugs.]	Article to the public because of media referring to problems with the antidepressants.
2003	Meeting of the CSM Expert group on the safety of SSRIs held on Tuesday 22nd July.	The group commented that it was a challenge to disseminate the information [about withdrawal reaction] in	Minutes

		such a way that informed patients of the risks but did not stop them taking the medication.	
2003	Committee on Safety of Medicines	No strong evidence has been identified to suggest that SSRIs cause other features of dependence.	Minutes
2003	WHO Expert Committee on drug dependence WHO Techical Report series no 915. Thirty third report. WHO Geneve.	Three SSRIs are among the 30 highest-ranking drugs in the list of drugs for which drug dependence has ever been reported to the Uppsala Monitoring Centre database.	Technical report
2003	Meeting 16 September CSM and Expert group on Safety of SSRIs	The group expressed concern about the lack of data on the long-tern effect of SSRIs and recommended that further research on this area was required.	Minutes
2003	Committee on Safety of Medicines and Expert Group on Safety of SSRIs. Minutes of the meeting held Tuesday 25 November 2003. http://www.mhra.gov.uk/home/groups/pl-p/documents/committeedocument/con003487.pdf	Professor Drummond explained that he had considered to what extent the SSRIs meet the ICD-10 and DSM-IV definitions of dependence and has concluded that the extent to which SSRIs meet the criteria is much less than with other typically dependence producing drugs.	Minutes
2003	Interim report of the Committee on Safety of Medicines´ Expert Working Group on Selective Serotonin Reuptake Inhibitors September 2003	Two areas of continual concern …. and withdrawal reactions on stopping SSRIs.	Report
2003	WHO Pharmaceutical Newsletter 2003; no 1. Drugs of abuse: Problems of data collection, definitions and liability assessment.	However, such a conclusion may only be drawn after a careful review of the significant number of "drug dependence" reports for SSRIs received by the ADR monitoring system and, not on the basis of the terminology discussion that withdrawal reactions by themselves are insufficient to imply dependence.	Newsletter
2004	Committee on Safety of medicines URL:http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf	There is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome according to internationally accepted criteria (either DSM-IV or ICD-10)	Scientific report
2004	Committee on Safety of Medicines, Expert Group on Safety of SSRIs. Tuesday 9 November 2004.	A proportion of SSRI withdrawal reactions are severe and disabling to the individual.	Minutes
2005	Danish Medicines Agency (20 June 2005). Summary of Product Characteristics for Seroxat (paroxetine). http://www.produktresume.dk/docushare/dsweb/Get/Document-	[Occurrence of discontinuation symptoms does not imply that the drug is addictive or cause	Summary of Product Characteristics

	21876/Seroxat%2C+filmovertrukne+tabletter+20+mg+og+30+mg.doc	dependence.]	
2005	European medicines Agency Doc. Ref. EMEA/CHMP/PHVWP /397128/2005	Generally these events[withdrawal symptoms] are mild to moderate and are self-limiting, however in some patients they may be severe and/or prolonged.	Core SPC Wording for SSRIs

The first warnings about dependence with benzodiazepines came approximately 20 years after the first report showing withdrawal symptoms. This warning was based on the belief by the authorities that very few people were dependent. In contrast to this, it only took 5 years before it was communicated that withdrawal reactions were connected to SSRIs. In the meantime, however, the definition of dependence had been changed with the consequence that symptoms that formed the benzodiazepine dependence also formed the SSRI withdrawal reactions. For a longer period it was the perception of the authorities, that SSRIs withdrawal reactions only affected few patients and that the symptoms were relatively mild.

There is interesting literature pertaining to the regulation of the newer antidepressants (60). It is described that the regulatory inertia was illustrated through the 2004 CSM Expert Working Group on the safety of SSRIs (61). The report pointed to lack of evidence of risk, because a number of essential studies had never been performed. Still, 10-15 years after licensing the SSRIs, the MHRA had received no convincing evidence of the incidence of SSRI withdrawal reactions.

Patients reported symptoms as dependence to the SSRIs, but as the dependence definition was changed in 1987, as shown in study 2 in this thesis, the reported symptoms were not recognised as dependence but as withdrawal syndrome. However, in the WHO Uppsala Monitoring Centre database three SSRIs were among the 30 highest-ranking drugs in the list of drugs for which dependence has ever been reported by June 2002 (62).

We related the findings in the documents to the risk management principle, described in legislation, and the precautionary principle, described in literature.

In the light of the precautionary principle and the risk management principle, the results of our study can be understood in two ways. Seen from a precautionary principle, the drug agencies have

failed to acknowledge that SSRIs can cause dependence, with reference to the diagnostic disease manuals ICD-10 and DSM-IV, and have prepared conservative estimates with regard to the severity and the number of people affected. In this perspective, changes in the communication from drug regulators to the public about adverse effects happened slowly.

Seen from a risk management principle, the drug agencies have reacted in concordance with the slowly growing knowledge of adverse drug reactions and have sharpened the information to the public over time. However, relying on spontaneous reporting of adverse effects leads to underrecognition and delayed information about the problems. In light of the history of other psychoactive drugs, e.g. benzodiazepines and barbiturates, it is nonetheless surprising that the regulatory bodies have not required studies from the manufacturers that could elucidate the dependence potential of the SSRIs before marketing authorization.

There is consistency between the studied documents with regard to the announcement that SSRIs do not create dependence. We did not exclude any documents that could enlighten the objective of this study and that had content relevant for the study objective.

Discussion

A limitation of this study was the analysis of the documents, as the data could be misinterpreted. The documents are written in an organisational and historical context and read, understood and analysed in a new context. The documents were not written for research purposes but were written mainly as documentation, information or as statements. There is a risk that data have been analysed in the light of the historic development since the documents were written.

It might be supposed that the documents are written by professional document makers in the drug agencies, and with a view to the risk that a trivial bureaucratic document could be used in a critical case about the institutions management practice. The documents have all been through a careful writing process.

Abraham and Davis have explored drug regulation in several studies demonstrating regulatory passive decision-making and accept of drug risks, which were largely unknown to the public (63) McGoey has identified “a will to ignorance” within regulatory bureaucracies with SSRIs risk and benefit balance as a case (64). Healy has also studied drug regulation in relation to the SSRIs and concludes that in the case of the SSRIs the current regulatory practice overstates the benefits and underestimates the risks of drugs (65). John Abraham (66) has suggested that drug regulatory decision-making may be understood in the light of a permissive principle, i.e. a tendency to permit a technology on the market, even if it does not meet established standards of efficacy and safety and in contradiction to the precautionary principle. Abraham (67,68) found that drug regulators tend to weigh the balance of scientific doubts about drug safety in favour of the manufacturer, both pre- and post-marketing. Further the report from the UK House of Commons describes several problems related to the close relation between the pharmaceutical industry and the regulatory body (60).

7. Conclusion

The sales of psychotropic drugs have fluctuated widely over a 37-year period. We believe that the decline in sales of benzodiazepines was primarily due to the recognition that they cause serious dependency and by initiatives at a national level to curb their use, and that the recent steep increase in sales of SSRIs is a direct consequence of marketing pressures, as the effect of the SSRIs is overestimated (7,8).

The withdrawal reactions to SSRIs were very similar to those for benzodiazepines. It therefore makes no sense to describe only the latter as dependence symptoms.

In the light of the two models, the precautionary principle and the risk management principle, the results of this study could be understood in two ways. In the perspective of the precautionary principle, it could mean that the drug agencies have refused to acknowledge that SSRIs can cause dependence, with reference to the diagnostic disease manuals ICD-10 and DSM-IV, and minimised the problem with regard to the severity and the number of people affected. In this perspective, changes in the communication from drug regulators to the public about adverse effects happened slowly. In the perspective of the risk management principle, it could mean that the drug agencies have reacted in concordance with the slowly growing knowledge of adverse drug reactions and have sharpened the information to the public over time. The spontaneous reporting of drug adverse effects is characterised by underreporting, which is the main cause for the slowly growing knowledge of adverse effects. In the light of the history of other psychoactive drugs, e.g. benzodiazepines and barbiturates, it is nevertheless surprising that the regulatory bodies have not required studies from the manufacturers that could elucidate the dependence potential of the SSRIs before marketing authorization was granted.

8. Perspectives

Patient safety is at stake but is up against other interests, particularly commercial ones. Medawar and Hardon (29) ask if medicines are out of control and they summarize their concerns about conflicts of interests, pathogenic institutional secrecy, manipulation of data and results about drugs, ignorance to valuable information from patients about adverse effects, drug promotion through disease awareness campaigns, and medicines existing in a trade and economic discourse. Unfortunately, in this scenario it seems difficult to bring patient safety up front.

Advisory and decision making processes related to adverse effects and risk-benefit ratios are mainly influenced by scientists, experts and public officers in drug agencies. This might not be satisfactory from a public point of view, as the acceptability of adverse effects and risk-benefit ratios imply a range of cultural and social implications that might not be included in assessments by health professionals.

It is modest what is known about citizens' perspective on adverse effects of drugs. This needs further research.

Drug regulation models based on a precautionary principle or a risk management principle, respectively, can offer a different focus on patient safety. It has been mentioned that, if a precautionary principle is chosen, this might have consequences for the pharmaceutical industry´s willingness to develop new drugs.

There seems to be a problem with the pharmacovigilance system, as it is partly built on the spontaneous reporting of adverse drug reactions, which are under-reported. For some years, it has been possible for patients also to report adverse drug reactions directly to the regulators in several countries. This system might be developed further, as more research is undertaken on this issue.

In the perspective of a risk management model of drug regulation, it is assumed that the risks associated with the use of a drug can be measured scientifically and that the significance of the risks can be quantified. It is, however, only the user of the drug who can determine the acceptability of adverse effects and of the benefit / risk balance.

A problem that has only been briefly mentioned in this thesis is the willingness of doctors to prescribe these drugs. In the case of benzodiazepines, this willingness of prescribing declined through initiatives from the authorities. Several facts may be involved in the prevailing prescribing tradition, e.g. patients' expectations, doctors' education, and co-operation, involvement with, and conflicts of interests in relation to the pharmaceutical industry. This issue also needs further research.

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Paper 1

An analysis of psychotropic drug sales. Increasing sales of selective serotonin reuptake inhibitors are closely related to number of products. International Journal of Risk & Safety in Medicine, 2011; 23 (2): 125-32.

Correction to paper 1: page 128: Sales figures for the specific neurotransmitter reuptake inhibitors (N06AB and N06AX) separately were available form 1992. This is incomplete expressed, because N06AX also includes Mianserin, which is a receptor blocking agent and not a specific neurotransmitter reuptake inhibitor.

Paper 2

What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors.

Nielsen M, Hansen EH, Gøtzsche PC.

Addiction. 2012 May;107(5):900-8. doi: 10.1111/j.1360-0443.2011.03686.x. Epub 2012 Jan 23. Review.

Paper 3

Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did the health authorities react?

Authors: Margrethe Nielsen, Ebba Holme Hansen, Peter C. Gøtzsche

International Journal of Risk & Safety in Medicine 23 (2011) 125–132
DOI 10.3233/JRS-2011-0526
IOS Press

An analysis of psychotropic drug sales. Increasing sales of selective serotonin reuptake inhibitors are closely related to number of products

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Abstract. *Background:* Prescribing of selective serotonin reuptake inhibitors (SSRIs) has increased dramatically.

Objective: To compare the sales of benzodiazepines and SSRIs within the primary care sector in Denmark and relate changes in usage to number of indications and products on the market.

Methods: We used data from various sources to establish the sales curves of psychotropic drugs in the period 1970 to 2007, based on the Anatomic Therapeutic Classification system and Defined Daily Doses.

Results: Fluctuations in sales of psychotropic drugs that cannot be explained by disease prevalence were caused by changes in sales of the benzodiazepines and SSRIs. We found a decline in the sales of benzodiazepines after a peak in 1986, likely due to the recognition that they cause dependence. From a low level in 1992, we found that the sales of SSRIs increased almost linearly by a factor of 18, up to 44 DDD per 1000 inhabitants, which was closely related to the number of products on the market that increased by a factor of 16.

Conclusions: Sales of antidepressant drugs are mainly determined by market availability of products indicating that marketing pressures are playing an important role. Thus the current level of use of SSRIs may not be evidence-based, which is supported by studies showing that the effect of SSRIs has been overestimated.

Keywords: Benzodiazepines, SSRIs, DDD, sales, indications

1. Introduction

Psychotropic medicines have been available since the middle of the 1800s. Some of the active ingredients have changed over time and they have been associated with dependency [1, 2]. Barbiturates were introduced on the market in 1903 for treatment of insomnia and anxiety, but because of the risk of intoxication, dependency and drug abuse, they were slowly replaced by benzodiazepines, which have now been available for 50 years [1, 2]. At the peak of their use, the sales corresponded to a usage in about 10% of the Danish population [1], and they are still widely used, although the risk of dependency has been known for more than 25 years [1]. In 1988, selective serotonin reuptake inhibitors (SSRI) were

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introduced and expectations were high regarding efficacy and safety [2]. Benzodiazepines and SSRIs are partly registered for the same indications, for example anxiety [3].

Several studies have described an increasing use of SSRIs and a decreasing use of benzodiazepines. A few studies have looked at overall usage [1] and others have focused on specific drug groups [4, 5]. The OECD (Organisation for Economic Co-operation and Development) health data showed in 2007 that usage of antidepressants was increasing across the OECD countries [6].

The efficacy of the SSRIs has been questioned. In a meta-analysis of the newer antidepressants Turner et al. found publication bias in 74 FDA registered trials; published trials showed a 32% larger effects than when all trials in the FDA database were included [7].

Another recent meta-analysis showed that the SSRIs were only effective in severe depression (HDRS score of 25) whereas the effect was quite small for other degrees of depression [8].

2. Objective

Our primary aim was to compare the sales of SSRIs with that of benzodiazepines within the primary care sector in Denmark. We hypothesized that changes in sales of SSRIs were related to number of indications and number of products on the market.

3. Methods

We described the total exposure of the Danish population to psychotropic drugs, with a focus on benzodiazepines and SSRIs, and explored the possible reasons for the changes in sales.

We used data from Hansen and Gyldmark [1] for the period 1970–1981, Danish Drug Statistics for 1981–1991, data from Danish Medicines Information (DLI) for the years 1992 and 1993, and data from The Danish Medicines Agency (DKMA) for 1994–2007. The data for the whole period were based on the anatomic therapeutic classification (ATC) system and defined daily doses (DDD) indicated the exposure.

The ATC system is an internationally accepted classification system, which divides all medical products into 14 anatomical main groups, each with 2 therapeutic subgroups and 2 chemical subgroups [9]. We have processed data at the levels of the therapeutic main group (N05, N06), the therapeutic subgroup (N05B, N05C, N06A) and the chemical therapeutic subgroup (N05BA, N05CD, N05CF and N06AB, N06AX).

DDD is a technical unit expressing the typical maintenance dose for a drug given to an adult for its main indication. They are "defined" because they are chosen by experts on the background of theoretical considerations and pharmacological data, rather than from empirically based research of prescriptions and usage. DDD enable to some degree comparisons of usage over time and between countries [9]. Throughout this article, DDD refers to the number of inhabitants in treatment per 1000 per day (DDD/1000 inhabitants/day). We focused on the primary care sector because the general practitioners in Denmark prescribe by far most drugs. We related the DDDs and their development over time to the development in new indications and the number of products. The indications were obtained from the annual Drug Index, which are based on Summary of Products Characteristics, approved by the Medicines Agency prior to marketing.

We use the words sales and usage interchangeably, although it is not known how much of sold medicines are actually used.

We use the term psychotropic drugs about all drugs in ATC groups N05 and N06. These groups include antipsychotics, psychostimulants and antidementia drugs, which are used to a lesser extent compared to the drugs that we focused on: benzodiazepines and benzodiazepine-like drugs (N05BA, N05CD and N05CF), selective serotonin reuptake inhibitors (N06AB) and other antidepressants (N06AX). It appears from the Danish Medicines Agency annual drug statistics that these drugs represented about 84% of the sales of psychotropic drugs in 2007.

4. Results

Figure 1 shows the total exposure to all psychotropic drugs in the period 1970 to 2007. It increased from 120 DDD in 1970 to 138 in 1980, decreased to 82 DDD in 1993 and increased again to 125 in 2007. Thus, if we ignore the fact that some patients receive more than one drug simultaneously, this means that between 8 and 14% of the Danish population could have been exposed to some kind of psychotropic drug in this time span.

The sales in ATC group N06, which is dominated by antidepressants, was low until 1992, when a steep increase began, from 10 DDD in 1992 to 72 in 2007. It is because of this increase that the total sales of all psychotropic drugs went up again, as the sales in ATC group N05, which is dominated by benzodiazepines, continued to decline.

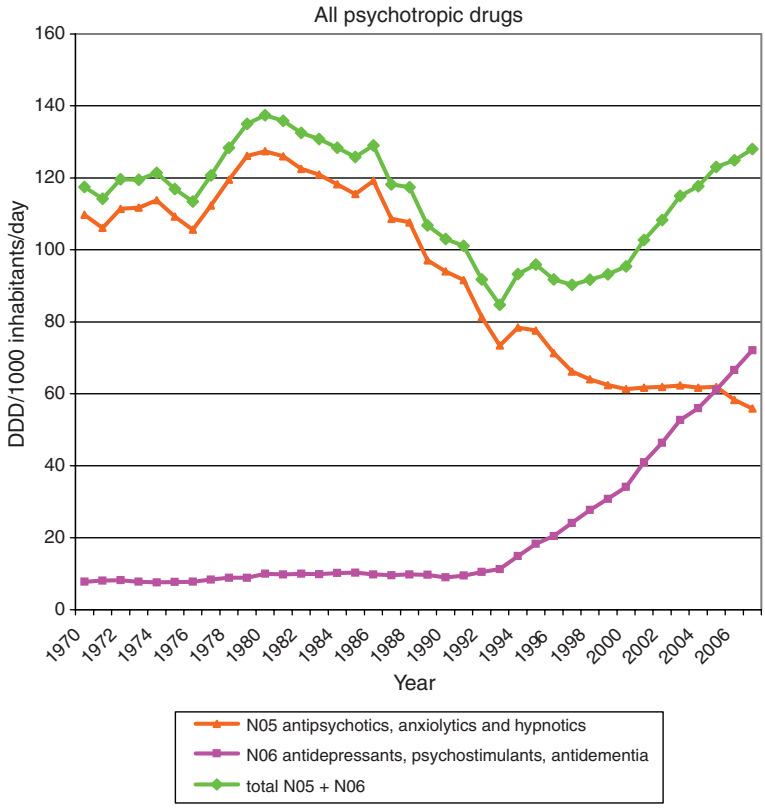

Fig. 1. Sales of all psychotropic drugs in DDD.

Sales of benzodiazepines peaked in 1986 (Fig. 2). Thereafter, there was a pronounced decline in sales that became less pronounced from about 1995, coinciding with increased availability of benzodiazepine-like drugs (N05CF) on the market.

Sales figures for the specific neurotransmitter reuptake inhibitors (N06AB and N06AX) separately were available from 1992. The recent steep increase in sales in ATC group N06 was entirely due to increased sales of these drugs (Fig. 2).

From 1992 to 2007, DDD for the SSRIs increased from 2.5 to 43.9, i.e. by a factor of 18. A closely similar increase was seen in the number of different SSRI products on the Danish market, including brands and generics, which increased in the same period from 3 to 47, i.e. by a factor of 16 ($r = 0.97$ for the correlation) (Fig. 3). Twenty-three different drug companies marketed the 47 different products in Denmark in 2007. The number of indications for treatment with SSRIs increased from 1 in 1992 to 8 in 2008.

In contrast to the SSRIs, there seemed to be no relation between sales of benzodiazepines and benzodiazepine-like drugs and number of products on the market. Sales started dropping in 1986 whereas number of products continued to increase up to 1996, where it peaked with 48 products, and then declined (Fig. 4). The number of indications increased from 8 in 1983 to 11 in 2005.

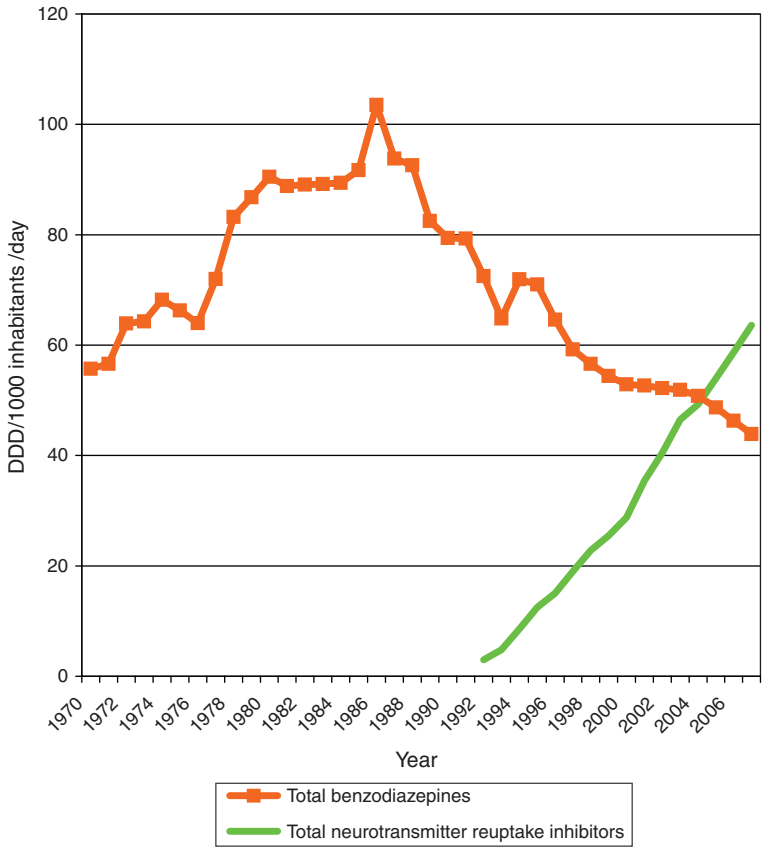

Fig. 2. The total sales of specific neurotransmitter reuptake inhibitors and total benzodiazepines and benzodiazepine-like drugs 1970–2007.

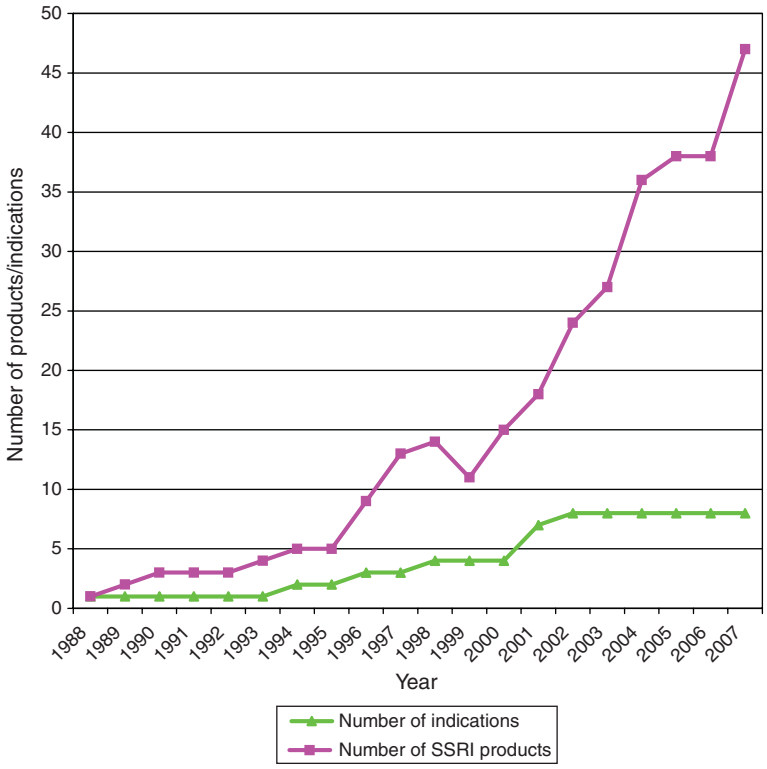

Fig. 3. Number of SSRI products and indications.

5. Discussion

We found that the fluctuations in overall use of psychotropics were mainly explained by changes in the sold amount of benzodiazepines and SSRIs. Usage of benzodiazepines declined, whereas usage of SSRIs increased almost lineary, closely related to a similar increase in the number of products on the market.

Our study covers 37 years, which allowed us to identify the most likely reasons for the observed fluctuations. One would expect the prevalence of serious psychiatric diseases, such as major depression, to be relatively stable over this period. The Diagnostic, Statistical Manual of Mental Diseases (DSM) has contributed with several new indications over this period, but this would be expected to lead to a stable increase in usage, and not to large fluctuations such as those we observed [10].

Benzodiazepines and SSRIs by far dominated the sales of psychotropic drugs in the studied time period. The peak in sales of psychotropic drugs in 1980 that was followed by a marked decline parallelled the sales of benzodiazepines. There seems to be two explanations for this decline. First, although serious dependency was documented already in 1961, it was not generally accepted until 20 years later [11]. Second, since 1980, the Danish National Board of Health has taken several initiatives to reduce usage of benzodiazepines targeting both patients and general practitioners. The initiatives involved withdrawal of reimbursement of the patients' expenses for benzodiazepines, requests to the general practitioners to reduce prescriptions of benzodiazepines, and withdrawal of 10 mg diazepam tablets from the market [1, 2].

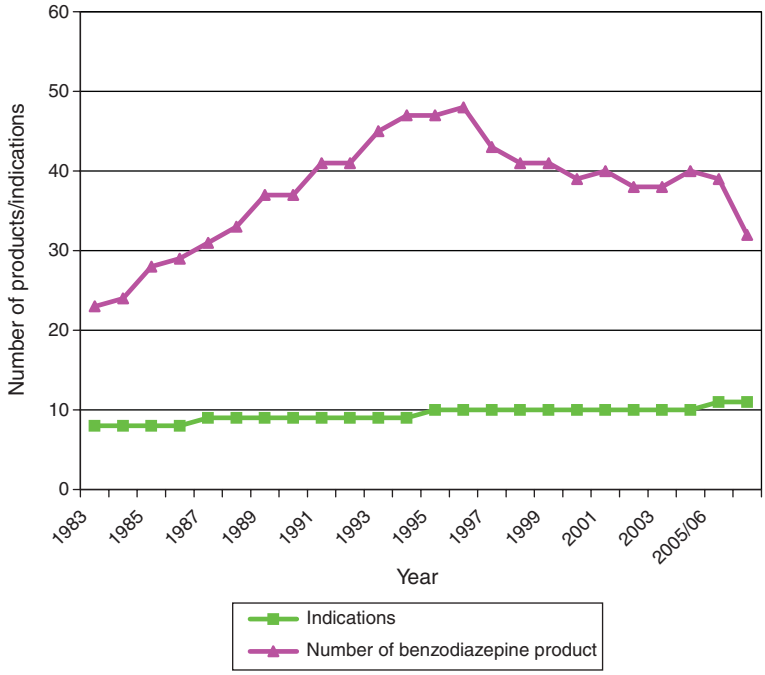

Fig. 4. Number of benzodiazepine products and indications.

In contrast, we found a steep and linear increase in sales of specific neurotransmitter reuptake inhibitors (N06AB and N06AX), which showed no signs of wearing off. This increase was mainly due to increased sales of SSRIs. Some of the indications for benzodiazepines and SSRIs are the same, but as the increase started several years later than the decrease in sales of benzodiazepines, the development cannot be explained merely by patients being transferred from one drug group to the other.

The most likely explanation for the increase in sales is increased marketing pressure. The number of products on the market increased steeply, at about the same rate as the increase in sales, and involved an increasing number of companies so that in 2007, 23 different drug firms marketed SSRIs (Fig. 3). General practitioners were therefore exposed to a steeply increasing number of sales pitches from drug representatives recommending SSRIs for an increasing number of indications. A Danish study has shown that general practitioners in general receive a median of 19 visits from drug representatives during six months and that the drug industry uses a variety of methods to get their message across including gifts, drug samples and invitations to courses and meetings [12]. Marketing is also directed towards potential patients through disease awareness campaigns [13]. This is indirect marketing, as direct marketing for prescription drugs aiming at consumers or patients is not allowed in the European Union. Disease awareness campaigns focus on a specific disease and its symptoms, with a request to see a doctor and with a drug company as sender, sometimes together with a patient organisation.

In 2007, the total sales of specific neurotransmitter reuptake inhibitors in Denmark, which has a population of 5.4 million people, amounted to about 75 million Euros. From the Danish Drug Statistics (2005–2009) it appears that two of these drugs were represented on the list of the 25 most sold drugs in Denmark, venlafaxine with total sales of 28 million Euro (14 million DDD) and escitalopram with total sales of 20 million Euro (20 million DDD). The widespread use of these expensive drugs suggests that

the treatment is not evidence-based. For example, escitalopram is almost 20 times more expensive than citalopram, even though the chemically active ingredient is the same.

The change in treatment of anxiety disorder, from benzodiazepines to newer antidepressants, has happened despite a lack of evidence in support of this change, and marketing strategies could therefore have played an important role [14]. This change in prescription habits might have opened the market for new antidepressants.

Guidelines have urged drug treatment of depression and anxiety [15, 16] and have emphasized the risks of under-treatment. They are often influenced by the companies' marketing strategies and those who write them usually have numerous conflicts of interest in relation to receiving industry money [17]. More than 60% of the doctors participating in the working group on the Danish depression guideline had financial ties to the pharmaceutical industry [15, 18].

The prevalence of psychiatric disease and distress should also be interpreted in the light of changes in diagnostic and classification systems and a new symptom-based approach to substantiate the diagnosis as described in the Diagnostic, Statistical Manual of Mental Diseases III [19]. New disorders have been included and existing disorders 'exploded', e.g. anxiety neurosis was split into seven new disorders [19]. The symptom-based approach has been criticized for creating diseases, classifying normal life distress and sadness as mental disease that should be treated with drugs [19]. The symptoms described as criteria for depression are now broad, for example fatigue, insomnia or diminished ability to concentrate, and do not distinguish between a disorder and expected reactions to a situational context, for example the loss of a beloved person with symptoms persisting for more than two months [19]. Further other life crises like divorce, serious disease or loss of job are not mentioned as exclusion criteria [19]. Thus, it is likely that changes in the diagnostic classification systems have contributed to the increased sales of SSRIs, and that part of this increase represents over-diagnosis and over-treatment. This is further supported by the fact that 56% of the DSM IV overall panel members had financial ties to the pharmaceutical industry, and in the panel on "mood disorders", 100% had such ties [20]. This indicates serious problems with conflicts of interests, not least because the ties were especially strong in those diagnostic areas where drugs are first line of treatment.

5.1. Strengths and weaknesses

We combined statistics from different time periods, based on varying ATC levels, which gave us the possibility to present data for usage at an overall level. The three different data sources all used ATC and DDD, and there are some overlaps between the data sources, which confirmed the reliability of the data. Data from the secondary sector are not included in the analysis, as prescription is low and therefore not important for the overall picture. Our data are on sales, which cannot be equated with usage. Another limitation is that the data were available as DDD, but the defined daily dose might be lower or higher than the average dose of a drug in practice. For example the DDD for citalopram is 20 mg [9] but the recommended dose varies between 10 mg and 60 mg [3].

6. Conclusion

The sales of psychotropic drugs has fluctuated widely over a 37-year period. We believe that the decline in sales of benzodiazepines was primarily due to the recognition that they cause serious dependency and by initiatives at a national level to curb their use, and that the recent steep increase in sales of SSRIs is a direct consequence of marketing pressures, as the effect of the SSRIs is overestimated [7, 8].

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Conflicts of interest

None declared.

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Addiction

REVIEW

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What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors

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ABSTRACT

Aims To explore the rationale for claiming that benzodiazepines cause dependence while selective serotonin re-uptake inhibitors (SSRIs) do not. **Methods** We analysed the definitions of dependence and withdrawal reactions as they had appeared over time in the *Diagnostic Statistical Manual of Mental Diseases* (DSM) and the *International Classification of Diseases* (ICD). We also compared the discontinuation symptoms described for the two drug groups in a systematic review. **Results** The definition of substance dependence has changed over time in both the DSM and ICD. In the most recent classifications several criteria, including behavioural, physiological and cognitive manifestations, must be fulfilled. This change was published with the revision of the DSM-III revision in 1987 (DSM-IIIR), after the recognition of benzodiazepine dependence and just before the SSRIs were marketed in 1987–88. We found that discontinuation symptoms were described with similar terms for benzodiazepines and SSRIs and were very similar for 37 of 42 identified symptoms described as withdrawal reactions. **Conclusions** Withdrawal reactions to selective serotonin re-uptake inhibitors appear to be similar to those for benzodiazepines; referring to these reactions as part of a dependence syndrome in the case of benzodiazepines, but not selective serotonin re-uptake inhibitors, does not seem rational.

Keywords Benzodiazepine, dependence, DSM, ICD, SSRI, withdrawal reactions.

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INTRODUCTION

In a historical perspective, it has been well described that psychotropic drugs may cause withdrawal reactions. Benzodiazepines were marketed at the beginning of the 1960s, primarily for the treatment of anxiety and insomnia. Already in 1961, a study documented dependence with benzodiazepines [1]. Two decades later, in 1980, the addictive characteristics of benzodiazepines were recognized by the authorities, although at the beginning as only a minor problem, because they had received few spontaneous reports on dependence [2]. In 1988, after publication of many studies, the true extent of the problem was acknowledged by the authorities [3]. The usage increased dramatically until the 1980s, and then decreased because of their dependence potential [4].

For antidepressants, withdrawal reactions were first reported with imipramine, a tricyclic antidepressant (TCA), in 1959 and were described in detail in 1961 [5]. Subsequent studies reported that withdrawal reactions also occur with other TCAs and with the monoamine oxidase inhibitors (MAOIs) [6]. The selective serotonin re-uptake inhibitors (SSRIs) were launched in the late 1980s and were marketed for some of the same indications as benzodiazepines; for example, anxiety and phobia. From 1991 and onwards, case reports [7–11] about withdrawal reactions following use of SSRIs were published and concern was raised that these drugs might

cause dependence [4]. The withdrawal syndrome was characterized by specific physical and psychological symptoms. However, just as for the benzodiazepines, SSRI withdrawal symptoms were described by the authorities as being rare and relatively mild [12], and the usage of SSRIs has been increasing rapidly since their marketing, with no signs of levelling off [13].

In 2006, Richard Shelton [14] described that abrupt termination of treatment with SSRIs can result in a discontinuation syndrome characterized by symptoms such as anxiety, crying, dizziness, headache, increased dreaming, insomnia, irritability, myoclonus, nausea, paraesthesias and tremor. This syndrome is not specific to SSRIs, as similar phenomena have been reported for at least 21 different antidepressants over the last 5 decades [14].

Peter Haddad noted in 2005 [15] that medical authorities do not regard antidepressants as causing dependence, but that this view had been challenged because SSRIs and other antidepressants cause withdrawal symptoms that impede treatment discontinuation in some patients. Further, Haddad mentioned that the terms 'discontinuation' and 'withdrawal syndrome' are both being used. Discontinuation is the preferred term among those with vested interests who do not wish to regard antidepressants as addictive, while others perceive this term as misleading. In many people's minds, withdrawal syndrome is synonymous with dependence while discontinuation syndrome is more neutral [15].

Aim

The aim of our study was to explore the rationale for claiming that benzodiazepines cause dependence, while SSRIs do not.

MATERIAL AND METHODS

We reviewed the definitions of dependence and withdrawal reactions, as they have appeared and changed over time, in the *Diagnostic Statistical Manual of Mental Diseases* (DSM) and the *International Classification of Diseases* (ICD). We extracted data from DSM-III published in 1980 [16], DSM-IIIR from 1987 [17], DSM-IV from 1994 [18] and the ICD-10 from 1992 [19]. All the DSMs can be found on the internet [20]. Data on changes in the definitions of dependence and withdrawal reactions, including criteria for type, number and duration of symptoms, were extracted by one author (M.N.).

Further, we conducted a systematic literature search in PubMed for descriptions of symptoms of benzodiazepine dependence and SSRI withdrawal reactions. We performed a search for each drug group, 'benzodiazepines (MeSH)' and 'serotonin uptake inhibitors (MeSH)', combining them with the term 'substance-related disorders (MeSH)'. The MeSH term 'substance-related disorders' includes terms such as dependence, addiction, abuse and drug habituation, and it also includes the MeSH term 'substance withdrawal syndrome', which is a term further down in the MeSH hierarchy. Reference lists of identified studies were scrutinized to identify further relevant studies. We included studies in English and included randomized trials, review articles and observational studies describing withdrawal or discontinuation symptoms in adults, and excluded case reports. One author (M.N.) screened the titles and abstracts of all publications. All potentially eligible publications were obtained as full publications and assessed for relevance and inclusion. One author (M.N.) extracted the data from the included publications. Figure 1 shows a flowchart of the literature search strategy.

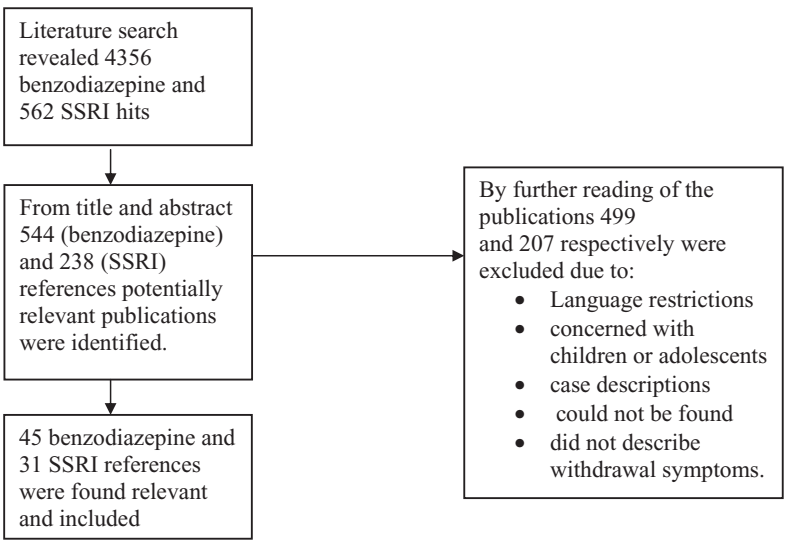

Figure 1 Search strategy

RESULTS

Definitions

In DSM-III, which was current in 1980 when benzodiazepines were recognized as being addictive, a diagnosis of dependence required either development of tolerance or withdrawal reactions (see Table 1 and Appendix S1; details of online supporting information are given at the end). Tolerance meant that increased amounts of the drug were required to achieve the desired effect. Withdrawal reactions meant a drug-specific syndrome following cessation or reduction in dose [16].

There was a substantial change of the definition in the revised manual in 1987 (DSM-IIIR). Dependence was now described as a cluster of behavioural, cognitive and physiological phenomena [17]. Tolerance and withdrawal reactions were among the manifestations, but they were no longer considered sufficient for the diagnosis (see Appendix S1 for details). Nine manifestation criteria were described (Table 1 and Appendix S1) and at least three of these should be fulfilled. A time criterion was also added, so that symptoms should have persisted for at least 1 month or should have occurred repeatedly over a longer time-period.

In DSM-IV, published in 1994, the nine criteria were reduced to seven, three of which must be present and must have occurred in the same 12-month period [18].

In ICD-10 from 1992, six criteria are described of which at least three must be fulfilled, occurring together for at least a month or repeatedly within a 12-month period [19].

The DSM-IV sourcebook, which aims at presenting the empirical evidence and associated rationales for decisions in the DSM-IV diagnosis manual and the discussions related to the decision [21], was published immediately after the manual. Participants involved in the development of the DSM-IV authored the sourcebook. It appears from the DSM-IV sourcebook that the DSM-III revision of dependence was based mainly on the alcohol dependence syndrome, which was taken to also be valid for drugs. The sourcebook has a chapter about 'Psychoactive substance dependence' and the reference list has 20 references to studies on such substances. However, 15 are to alcohol, three to opiates, one to narcotics and one to alcohol and opiates combined; there are no references to studies on psychoactive medicines. Concern was raised about the revised DSM-III definitions being so broad that other sorts of dependence could be included; for example, shopping dependence. Another important issue was that the diagnostic emphasis should again be placed on tolerance and withdrawal reactions, i.e. the physical aspects of dependence. It was even recommended for future revisions of the DSM [21], but this did not happen.

An important change from DSM-III to DSM-IV was that the phenomenon withdrawal reaction was listed not only as one of the criteria for dependence but also as an autonomous diagnosis at the same level as dependence. Withdrawal reactions are described in DSM-IV and ICD-10 as a group of symptoms of varying clustering and severity [18,19] (Table 2).

Symptoms of withdrawal or dependence

The literature search identified 4356 potentially relevant references about benzodiazepines and 562 about SSRIs. Of these, 45 and 31 relevant articles, respectively,

Table 1 Definition of dependence in the classification systems DSM and ICD.

	Manifestation criteria	*Time criteria*	*Number of manifestations required*
DSM-III (1980)	Tolerance to the substance or withdrawal symptoms	No time criteria	One
DSM-IIIR (1987)	Tolerance, withdrawal symptoms, much time spent to obtain the drug, not able to cut down use, uncontrolled use, continued use despite problems, normal activities are given up, the drug relieves withdrawal symptoms	One month or manifestations have occurred repeatedly over a longer period	At least three of the manifestations
ICD-10 (1992)	Tolerance, withdrawal symptoms, preoccupation with drug use, compulsion to take the drug, uncontrolled use, persistent use despite problems	One month or if less than a month then manifestations should have occurred together repeatedly within a 12-month period	Three or more of the manifestations
DSM-IV (1994)	Tolerance, withdrawal symptoms, much time spent to obtain the drug, not able to cut down use, uncontrolled use, continued use despite problems, normal activities are given up	Manifestations occur at any time in the same 12-month period	Three or more of the manifestations

Table 2 Criteria for substance withdrawal (source: DSM-IV).

(A)	The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy and prolonged
(B)	The substance-specific syndrome causes clinically significant distress or impairment in social, occupational or other important areas of functioning
(C)	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

described dependence or withdrawal reactions and were not case reports (Fig. 1).

We identified a range of symptoms (Table 3 and Appendix S2), many of them described in several ways, using different words. We adopted a categorization, which has been used previously for antidepressant discontinuation symptoms [6,22]:

- general symptoms
- gastrointestinal symptoms
- sleep-related symptoms
- balance-related symptoms
- sensory-related symptoms
- movement-related symptoms
- affective-related symptoms
- psychosis

According to this classification, we identified 42 symptoms, 37 of which were described for both benzodiazepines and for SSRIs. Three symptoms (palpitations, skin rash/itching and constipation) were described only for benzodiazepines and two (bouts of crying and parkinsonism) were described only for SSRIs. Symptoms for both drug groups appeared in all the above-mentioned categories, but for the benzodiazepines, the problem was categorized as dependence in accordance with DSM-III, and for the SSRIs as a withdrawal syndrome in accordance with DSM-IV and ICD-10.

DISCUSSION

The withdrawal reactions to SSRIs were very similar to those for benzodiazepines. It therefore makes no sense to describe only the latter as dependence symptoms.

The reluctance towards accepting that psychoactive drugs cause dependence can have serious clinical consequences. In 2008 approximately 100 000 patients in Denmark, in a population of only 5.5 million, were in long-term treatment with benzodiazepines, and many of them will require tapering of the doses over long time-periods if these drugs are ever to be discontinued [23].

It is remarkable that the bar for diagnosis of dependence was raised at about the same time as it became widely accepted that benzodiazepines lead to dependence, namely with the revision of the DSM-III in 1987 (DSM-IIIR). This change happened just before the SSRIs were marketed in 1987–1988.

Lack of validity of the change in definition

The change in definition of dependence in the DSM-IIIR was based on literature about alcohol, opiates and narcotics, and not about psychoactive medicine, although the symptoms are not the same [24]. It is also unfortunate that it gave rise to a new autonomous diagnosis of withdrawal reactions for those who did not fulfil the criteria for dependence.

Benzodiazepine dependence was based on the physical criteria described in DSM-III, tolerance and withdrawal reactions. The development of tolerance was described in 1980 [2], but this was later questioned with respect to the anxiolytic effect [25], and clinical evidence supports the idea that tolerance develops selectively to different drug effects [26,27]. This means that benzodiazepines do not always fulfil the two criteria of tolerance and withdrawal reactions described in DSM-III.

It has also been suggested that SSRIs lose efficacy during maintenance treatment [28–30]. Some have suggested a pharmacokinetic tolerance reducing the concentration of the drug or its duration of action, while others have suggested pharmacodynamic processes changing the sensivity to the drug [31]. Thus, in some cases SSRIs fulfil the criteria of tolerance and if they had been marketed 8 years earlier they would therefore have fulfilled the dependence criteria existing at the time. An additional similarity is that not only benzodiazepines can cause dependence at therapeutic doses; we found that this is also the case for SSRIs.

The validity of the dependence criteria in DSM-IV and ICD-10 is also questionable, as they are the same for substances as diverse as alcohol, amphetamine, opiates, cannabis, cocaine, caffeine, inhalant substances, nicotine and sedative, hypnotic and anxiolytic drugs. There is also room for some flexibility. According to DSM-IV, three out of seven criteria must be met, but in the introduction to the DSM-IV it is recommended to use one's clinical judgement about the number of criteria [32].

The general lack of a research and evidence-based approach in the development of the DSM has been described by Caplan [32], Kutchins & Kirk [33] and Lane [34]. This deficiency has resulted in inclusion and exclusion of diagnoses based on subjective, political or other reasons than scientific ones. For example, the criteria for the various diagnoses in the DSM-III and III-R were built on questions to psychiatrists about which criteria for a given category they found useful and whether they had other suggestions. This process was rather subjective and not evidence-based [32]. Concern about the dependence criteria has also been raised by Voyer [35,36]. He

Table 3 Signs and symptoms of withdrawal from benzodiazepine and selective serotonin re-uptake inhibitors (SSRIs) (result of literature review).

	Benzodiazepines	*SSRIs*
General	Influenza-like symptoms	Flu-like symptoms
	Diaphoresis, sweating, flushing	Sweating
	Headache	Headache
	Fits, convulsions, seizure	Convulsions
	Muscle aches, muscular pains	Myalgias
	Fatigue, lack of energy, lethargy	Lethargy, fatigue, somnolence
	Stiffness	Arthralgias
	Palpitations	
	Skin rash, itching	
Gastrointestinal	Abdominal pain, abdominal cramps	Abdominal cramping, abdominal pain
	Nausea, vomiting, dry retchings	Nausea, vomiting
	Loss of appetite, weight loss, anorexia	Appetite disturbance, anorexia
	Diarrhoea, constipation	Diarrhoea
Sleep	Sleep disturbance	Sleep disturbance
	Nightmares	Nightmares, vivid dreaming
Balance	Ataxia	Ataxia
	Dizziness	Dizziness
	Lightheadedness	Lightheadedness
	Vertigo	Vertigo
Sensory	Blurrred vision, difficulty in focusing	Blurrred vision, visual disturbance
	Sore eyes	Sore eyes
	Feeling of electric shocks, pins and needles	Electric shock sensations
	Numbness	Numbness
	Parasthesia, muscle twitches, tingling, altered sensation, fasciculation	Parasthesia, restless legs, tingling
	Increased acuity to sound, smell, touch, pain, tinnitus, hyperosmia, photophobia, hyperaccusis	Tinnitus, rushing noise in head
	Altered taste, metallic taste in mouth,	Taste perversion
Movement	Jerks, myoclonic jerks, jumpiness	Myoclonic jerks
	Tremor, tremulousness, shakiness	Tremor, shaking
	Incoordination, impaired perception of movement	Imbalance, unsteady gait
		Parkinsonism
Affective	Agitation	Agitation
	Aggression	Aggression, anger
	Irritability, restlessness	Irritability
	Mental tension	Feeling tense
	Anxiety, panic attacks, agoraphobia, dysphoria	Anxiety, sudden panic
	Depressed mood, depression	Low mood, emotional lability, depression
	Nervousness	Nervousness
	Depersonalization	Depersonalization
	Derealization, perceptual disturbance, paranoid reaction, delirium	Detachment
	Confusion	Confusion
	Poor concentration	Decreased concentration, slowed thinking
	Poor memory	Memory problems, amnesia
		Bouts of crying
Psychosis	Hallucination	Hallucination
	Delirium	Delirium
	Psychosis	Catatonia

No reference mentions all signs or symptoms.

found that although a quarter of the elderly population included in his study were prescribed benzodiazepines, with a mean duration of 9 years and in contradiction to prescription recommendations of short-term use (2–3 weeks), only 9.5% of the benzodiazepine users met the DSM-IV criteria for dependence. This contrasts with the finding that long-term use of benzodiazepines, generally defined as longer than 6 months, may be explained primarily by the development of dependence, as benzodiazepines lose some of their efficacy as anxiolytics or hypnotics after a few weeks of regular use [35].

An additional problem is that withdrawal reactions, according to DSM-IV, are observable substance-specific symptoms caused by discontinuation or reduction in substance use and which causes physical and psychological distress. In contradiction to this, the diagnosis of dependence is based on a number of criteria that do not necessarily present themselves as symptoms but as behavioural aspects and a compulsive pattern of drug use as premises for the diagnosis. The dependence criteria are not observable in the same way as withdrawal reactions and may lead to differential use of the diagnosis. There seems to be no consensus as to whether dependence is uni- or multidimensional, nor about how to measure it [37]. This is supported by the fact that the DSM diagnoses are the result of negotiations and consensus between experts and in that way social constructs.

Conflicts of interest

Strong financial ties between the DSM-IV panel members and the pharmaceutical industry have been revealed [38], and there are clear conflicts of interests involved in the choice of terms. For example, several psychiatrists deliberately use the term 'discontinuation reactions' as a euphemism instead of 'withdrawal reactions' [14,15,39,40]. They argue that it is important not to foster inadvertently the lay belief that antidepressants are addictive, as this might contribute to undertreatment of depression, and they also claim that discontinuation reactions do not indicate dependence [41].

The psychiatrists' opinions agree with the opinion of an Eli Lilly representative expressed at a meeting in the Committee on Safety of Medicines (UK) in 1998 [42]: 'The Committee was informed that Lilly (marketing authorization holder for Prozac) had expressed concern of the use of the term "withdrawal reaction" when referring to the symptoms occurring on withdrawal of treatment due to the fact that the term "withdrawal" has a specific meaning and implies that the drug is addictive. Lilly has suggested the use of the term "discontinuation reactions." ' The Committee did not accept this suggestion [42] but acknowledged, at a later meeting in 2003, that the semantics could be an issue: 'The group commented that it was a challenge to disseminate the information [about withdrawal reactions and dependence] in such a way that informed patients about the risks but did not stop them taking the medication' [43]. We take issue with such an unsolicited paternalism that does not seem to respect the principle of informed consent.

Drug regulators

The Committee for Proprietary Medicinal Products (CPMP) in the European Medicines Agency (EMA) concluded in 2000 that there was a lack of evidence for dependence because the available studies were not designed to study withdrawal phenomena in SSRIs [44]. We find this position highly questionable. This fact does not remove the problem, and the problem has been noted in many studies.

After dependence was shown for the barbiturates, benzodiazepines were marketed with the claim that they did not cause dependence. This was not true, and the drug regulators admitted later that these drugs did, in fact, cause dependence. The authorities should therefore have demanded precisely such studies that they noted in 2000 were not available, when they received marketing applications for SSRIs. Further, there were indications of possible addictive properties for antidepressants in studies that showed that their use could reduce intake of other addictive substances [44].

The United Kingdom's expert working group on the safety of SSRIs published a report in 2004 [45]. Data about withdrawal reactions were reviewed, including case reports, published studies, spontaneous reporting and clinical trial data from the marketing authorization holders. The conclusion of the review was that withdrawal reactions have been reported with all SSRIs; that there is some uncertainty about their true frequency; but also that they are sufficiently common and in some cases severe enough to justify initiatives to minimize them. The working group reviewed the published literature about the abuse and dependence liability, but confined itself to one literature review, four letters to the editor and a case report. These data were compared with the ICD-10 and DSM-IV dependence criteria. The SSRIs met two of six ICD-10 criteria: withdrawal reactions and patients preoccupied of having supply of the drug, and three of seven DSM-IV criteria: withdrawal reactions, the substance is taken over a longer period than intended because of difficulties stopping, and sometimes a desire to cut down can be unsuccessful.

On this delicate basis, the main conclusion was that the extent to which these criteria are met was much less compared to other typically dependence-producing drugs, and that the data revealed no evidence that these drugs are associated with dependence [45]. However, in contrast with this, the working group also concluded that

abrupt cessation from any psychoactive drug could be expected to result in a withdrawal reaction after a significant duration of use and that this can be explained by the pharmacological actions on the brain and the changes that occur when the drug is withdrawn [45]. It was mentioned that the benzodiazepines have been established clearly as drugs that may produce dependence, but not that the dependence definition had been changed and that several more criteria for the dependence diagnosis were added in the 1987 DSM-IIIR [45].

It is clear that the authorities' approach to warnings is somewhat conservative and is characterized by a permissive principle in contradiction to a precautionary principle [46].

In guidelines and treatment recommendations, the authorities have urged prescribers to use SSRIs as a first choice of treatment at the expense of benzodiazepines [47]. This may seem reasonable, as benzodiazepines are recognized as addictive, but we believe this recommendation is not evidence-based, as this would require direct comparisons of the two drug groups in randomized trials. Furthermore, substituting benzodiazepines with SSRIs required that SSRIs were not associated with dependence. This was obtained by using the term 'discontinuation reaction' rather than 'withdrawal syndrome', which is one of several criteria for dependence.

WHO's position

WHO has a very different view on the definition of dependence. WHO Drug Information from 1998 [48] described withdrawal reactions from SSRIs and discussed the difference between withdrawal reactions and dependence. The WHO defined dependence as 'a need for repeated doses of the drug to feel good or to avoid feeling bad' and noted that: 'When the patient needs to take repeated doses of the drug to avoid the bad feelings caused by withdrawal reactions, the person is dependent on the drug'. Most importantly, WHO mentioned: 'All unpleasant withdrawal reactions have a certain potential to induce dependence and this risk may vary from person to person. With increasing severity, the likelihood of withdrawal reactions leading to dependence also increases.' WHO's stance is supported by case reports about severe or persisting symptoms despite repeated attempts to taper therapy [49]. Furthermore, three SSRIs were among the 30 highest-ranking drugs in the list of drugs for which dependence has ever been reported to the WHO Uppsala Monitoring Centre database by June 2002 [50].

In our opinion, the WHO definitions are more straightforward, more pragmatic and less ambiguous than those in the diagnostic manuals and reflect patient experiences more clearly. We have explored how patients have described their experiences on the internet and in research articles. They use expressions such as 'weaning off', 'coming or to be off the drug', 'recovering from drug damage', 'addiction', 'dependence', 'the bluppering mess', 'body was reacting . . . bit like a junkie', 'living hell', 'how the hell can one get off these cursing tablets, I have failed three times at coming off it' and 'failed attempts to come off' [51–53].

Compare this with the change in the DSM-IIIR criteria from a merely physiological disorder, requiring either tolerance or withdrawal, consisting of observable symptoms, to a definition that reflects the importance of the substance in the individual's life focusing on behavioural aspects and a compulsive pattern of drug use. The new behavioural criteria must be a challenge for the clinicians to use and their relevance and the logic behind them can be discussed; e.g. benzodiazepines are said to induce dependence, but their use does not necessarily lead to drug craving as we know it from the opiates.

The withdrawal syndrome has also been a challenge in a clinical setting, in the beginning because patients presented with withdrawal symptoms that were not recognized but were often interpreted as a relapse of the depression. Later, the withdrawal syndromes required a tapering of dosage, to limit the symptoms for the patients and to get them off treatment.

Limitations of the study

There are few studies that report on the frequency and severity of the symptoms after withdrawal of SSRIs and benzodiazepines, and we could therefore only compare the type of symptoms. When comparing the two drug classes, it should be borne in mind that the individual drugs have different half-lives. For example, lorazepam has a short half-life compared to diazepam, and fluoxetine has a long half-life compared to paroxetine, which has the consequence that patients experience fewer withdrawal symptoms from interrupted fluoxetine treatment than for interrupted paroxetine treatment, as shown by Rosenbaum *et al.* [54].We did not include ICD-9 in our analysis because drug dependence is vaguely defined and could not add any value to our study.

Different scales and questionnaires focus on different symptoms. The findings seem to be somewhat robust, as so many studies describe very similar symptoms. For example, the typical SSRI withdrawal syndrome as described by Haddad [6] is quite similar to the typical benzodiazepine dependence syndrome described by Lader [55]. Although we performed a thorough literature search, including scrutinizing reference lists in identified papers, literature searches always have limitations, e.g. due to limitations in databases, limitations in search terms and access to documents. Hence, we cannot preclude that we have missed relevant references.

CONCLUSION

The withdrawal reactions to SSRIs were very similar to those for benzodiazepines. It therefore makes no sense to describe only the latter as dependence symptoms.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Dependence criteria.
Appendix S2 References.

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Dependence and withdrawal reactions to benzodiazepines and selective serotonin reuptake inhibitors. How did the health authorities react?

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Abstract

Aim: Our objective was to explore communications from drug agencies about benzodiazepine dependence and selective serotonin reuptake inhibitors (SSRIs) withdrawal reactions over time.
Method: Documentary study. We searched the web-sites of the European Medicines Agency and the drug agencies in USA, UK, and Denmark for documents mentioning benzodiazepines or SSRIs. We supplemented with other relevant literature that could contribute to this clarification. The searches were performed in 2009 in PubMed, Google, BMJ and JAMA.
Results: It took many years before the drug regulators acknowledged benzodiazepine dependence and SSRI withdrawal reactions and before the prescribers and the public was informed. Drug regulators relied mainly on the definitions of dependence and withdrawal reactions from the diagnostic psychiatric manuals, which contributed to the idea that SSRIs do not cause dependence, although it is difficult for many patients to stop treatment. In the perspective of a precautionary principle, drug agencies have failed to acknowledge that SSRIs can cause dependence and have minimised the problem with regard to the frequency and severity of the problem. In the perspective of a risk management principle, the drug agencies have reacted in concordance with the slowly growing knowledge of adverse drug reactions and have sharpened the information to the prescribers and the public over time. However, relying on spontaneous reporting of adverse effects leads to underrecognition and delayed information about the problems.
Conclusion: Given the experience with the benzodiazepines, we believe the regulatory bodies should have required studies from the manufacturers that could elucidate the dependence potential of the SSRIs before marketing authorization was granted.

No funding

Introduction

Today it is well documented that benzodiazepines can cause dependence, but for many years it was only discussed and not widely accepted. It also took some years before it was recognised that SSRIS can cause withdrawal reactions but today it is well described. It is well described that antidepressants and other psychotropic drugs may cause withdrawal reactions (1, 2). In 1961, Hollister, Motzenbecker & Degan (3) documented dependence with benzodiazepines. However, when benzodiazepines were first launched, the drug companies claimed that they did not have such effects (4). It is still being discussed whether SSRIs can also cause dependence.

Drug agencies play a very important role for reliable information about drugs. They are responsible for informing about efficacy and adverse effects of drugs, which is a prerequisite for informed consent when doctors prescribe drugs for patients. Society has an expectation that drug agencies will offer neutral and comprehensive information, also after marketing authorization is granted. Pharmacovigilance systems update information about adverse reactions, which may lead to regulatory action or changes in the information to prescribers and the public (5). Two different models of drug regulation are described. The first is the precautionary principle model and the second the risk management principle model (6). The precautionary principle has its focus on safety and effectiveness and accurate information to the public and prescribers. Even in absence of firm data about adverse events, signals should lead to delayed market authorization or restrictions. The risk management principle focuses on facilitating the industry’s possibilities to develop new drugs and market them quickly. The risk management principle holds that drugs should be assumed safe unless there is information to the contrary (6). These two paradigms are obviously in conflict, and the risk management principle has often been criticized. Abraham (7) suggested that drug regulation is permissive, Lader (8) talked about conservative drug regulation, and McGoye (9) described drug regulators' 'will to ignorance' in relation to safety issues.

There are different views whether SSRIs can cause dependence or not (10,11), and such controversy was also seen with the benzodiazepines (12). According to Peter Haddad (13), most medical authorities in the early 2000s do not think antidepressants could cause dependence, even though the European Medicines Agency (EMA) in 2000 (14) concluded that there was a lack of adequate studies and even though three SSRIs in 2002 were among the 30 highest-ranking drugs for which dependence has ever been reported to the Uppsala Monitoring Centre database (15). In 2012, we showed that the discontinuation symptoms of benzodiazepines and SSRIs are very similar (16). This suggests that both drug groups can cause dependence.

A few years after the introduction of SSRIs, concern was raised that they could cause dependence. This was confused, however, with a discussion about relapse of the disease, as withdrawal reactions are difficult to recognise and may be misinterpreted as incipient relapse (17). In the USA, paroxetine was marketed directly to consumers as "non-habit forming" (18).

It is therefore interesting to examine how drug agencies act when there is controversy. We studied how drug agencies communicated information about withdrawal reactions for benzodiazepines and SSRIs.

Aims

Our aim was to explore how changes in the adverse reaction profiles of benzodiazepines and SSRIs with respect to dependence and withdrawal reactions were reflected in the communications from drug agencies and other relevant health authorities to the prescribers and the public over time. Further, we evaluated the communications in light of the two models of drug regulation, based on a precautionary principle and a risk management principle (6).

Methods

Our study was based on documentary sources produced mainly by drug agencies as part of their regulatory tasks, including minutes from meetings, published articles, reports and other documents. We searched the web-sites of the drug agencies in USA (Food and Drug Agency, FDA), UK (Medicines Control Agency/Medicines and Healthcare Products Regulatory Agency, MCA/MHPR), Europe (European Medicines Agency, EMA) and Denmark (Danish Medicines Agency, DKMA) for documents mentioning benzodiazepines or SSRIs in order to study any trends in statements

about withdrawal symptoms and dependence. Further, we were open for other relevant literature that could identify relevant initiatives or statements. As a traditional focused search was not possible, we used a broad search strategy. The searches were performed between January and June 2009 in PubMed, Google, BMJ and JAMA, combining relevant search terms (figure 1). Documents were included if they concerned dependence or withdrawal reactions and expressed an agency's position, approach or initiative.

The regulators included in the study came from a wide geographical area and worked under varying legal frameworks. However, according to Lexchin (6), the regulatory decisions that different authorities make are often quite similar despite differences in origins, operating models, financial resources, and number of staff. We therefore expected that, by including several agencies, we would get a more robust, complete and consistent picture of drug regulators' approach.

Documents in health research can be accessed as a container of content but also as documents with a status, written in the context of an authority, and as an actor in the setting in which it is found. Our analysis focused on three document characteristics: the context of the document, the process that the document was a part of, and the facts that the document was a carrier of (20).

Results

We identified 6 documents related to the benzodiazepines and 23 documents for the SSRIs (table 2). All documents are official ones and convey drug regulators' and other health authorities' positions, i.e. they express one-way communication and are authoritative. A public and media focus on the SSRI withdrawal syndrome initiated a review process, during which working groups were established in drug agencies that referred to each other in the documents. References are shown in table 2.

Time to recognise adverse effects

Two papers from the Committee on Safety of Medicines (UK) from 1980 and 1988, an article from the Committee in 1993, and minutes from the Committee in 2004 (see table 2) showed that it took more than eight years for the UK regulators to accept the frequency and seriousness of the dependence potential of benzodiazepines, and ten years to accept withdrawal reactions as a class effect of SSRIs and that the symptoms can be serious.

In both cases, the source of the assessments was the spontaneous reporting system for adverse drug reactions, as shown in a systematic review by the Committee on the Review of Medicines (1980) and an article by Price et al. (1996).

Increasing frequency and seriousness of dependence and withdrawal reactions

The frequency and seriousness of the reactions related to benzodiazepines increased in the assessments over time. In 1980, the estimate of people suffering from benzodiazepine dependence was low, only 28 persons in the UK (Committee on the Review of Medicines, 1980), but in 1988, the risk of dependence was becoming "increasingly worrying" (Medicines Control Agency). From 1980, restricted use of benzodiazepines was recommended from 1980 (Committee on the Review of Medicines, 1980), i.e. short-term use, doses within the therapeutic range and gradual withdrawal. From the meeting minutes in the UK Medical Research Council, an estimate of the frequency of dependence appears low, but because many people used benzodiazepines, the number of dependent people was assessed to be around 10,000 – 100,000 people in UK (Medical Research Council Headquarters file 1980-82).

In 1993, withdrawal reactions on paroxetine were acknowledged and it was recommended that the drug should not be discontinued abruptly (Medicines Control Agency, 1993). In 1996, withdrawal reactions were described as "rare and not severe" (Price et al, 1996). In 1998, they were thought to be a "class effect" (Committee on Safety of Medicines, 1998) and in 2000, isolated reports of more serious symptoms were recognised (Medicines Control Agency, 2000). In 2004, a proportion of withdrawal reactions were thought to be "severe and disabling" (Committee on Safety of Medicines, 2004) and in 2005, they were described as "generally mild to moderate, self-limiting, but in some patients severe and prolonged" (European Medicines Agency, 2005).

Referring back to early warnings

By the time when the seriousness of benzodiazepine dependence and SSRI withdrawal reactions were acknowledged by the drug authorities, they referred back to earlier statements, but now labelled early warnings. For benzodiazepines, it was written in 1988 that, "there has been concern for many years," (Medicines Control Agency, 1988) referring to a statement in 1980, which, however, was that, "the true addiction potential of benzodiazepines was low" (Committee on the Review of Medicines, 1980). For SSRIs, drug authorities in 2000 stated that, "whilst the withdrawal symptoms reported were generally not serious, there have been isolated reports of more serious symptoms" (Medicines Control Agency, 2000) referring back to 1993, although the statements from that time were, "78 reports of symptoms occurring on withdrawal of paroxetine" and "it has been used extensively with around 370,000 prescriptions dispensed by the end of 1992" (Medicines Control Agency, 1993), suggesting that withdrawal reactions was not a problem.

SSRI dependence potential

The dependence potential of the SSRIs was consistently rejected by drug regulators. In 2000, EMA acknowledged that weak signals of addictive properties had been shown in some studies, but concluded that available evidence did not "suggest" that SSRIs cause dependence (European Medicines Agency, 1999/2000). Although the EMA stated that "the lack of evidence for dependence does not prove the absence of a problem," the dependence potential was rather firmly rejected, saying that, "SSRIs do not cause dependence" or "data do not indicate that SSRIs cause dependence" or "no strong evidence suggest that SSRIs cause dependence." It was noted that SSRIs "have been shown to reduce intake of addictive substances like cocaine and ethanol. The interpretation of this aspect is difficult."

In 1998, it was stated that SSRIs do not lead to dose escalation and drug seeking behaviour (Committee on Safety of Medicines, 1998) - two of the dependence criteria in Diagnostic Statistical Manual of Mental Disorders IV (21). In 2003, the symptoms of SSRI discontinuation were compared to the DSM-IV and ICD-10 dependence criteria (22), with the conclusion that the extent to which SSRIs met the criteria "is much less" than other dependence producing drugs (Committee on Safety of Medicines, 2003). Although drug seeking behaviour in relation to the SSRIs was acknowledged in 2004, and the review showed that the SSRIs met three out of the required three criteria for the diagnosis of dependence, the conclusion was similar to the 2003 conclusion (Committee on Safety of Medicines, 2004).

Different terms

Drug regulators use the term withdrawal reactions (e.g. Price et al, 1996; Medicines Control Agency, 2000). At a meeting in 1998 at the UK Medicines Agency in which representatives from the pharmaceutical industry participated, the marketing authorisation holders for Prozac (fluoxetine) expressed concern about using the term "withdrawal reaction" because it implied addiction, and suggested the term "discontinuation reactions". The drug regulators did not support this (Committee on Safety of Medicines, 1998).

Discussion

It took many years for drug regulators to recognize benzodiazepine dependence and SSRI withdrawal reactions. We shall discuss this, based on the two principles for drug regulation, the precautionary principle and the risk management principle. EU and US drug regulation is based upon the risk management principle (23, 24). This includes premarketing risk assessment, identifying and quantifying risks detected during clinical development, and that drug regulators evaluate how manufacturers assess potential risks.

Postmarketing risk management is based upon spontaneous adverse event reporting to the agencies from health professionals, patients, consumers and manufacturers. Drug regulators assess risk / benefit of market authorisation on the basis of this.

In contrast, according to the precautionary principle even weak signals, from the collection of adverse effects, rather than definite proofs, could lead to warnings or restrictions in the market authorisation.

Drug regulators have been guided by the definitions of dependence and withdrawal reactions in DSM-IV and ICD-10, but not consistently. For example, they preferred the term withdrawal reactions to the term discontinuation reactions, suggested by the pharmaceutical industry. But when SSRIs actually met 2 out of the required 3 criteria for the diagnosis of dependence, this was not accepted by drug regulators as dependence.

Spontaneous reporting of adverse effects

The pharmaceutical companies receive reports about adverse effects from doctors and drug regulators, assess a possible relationship to their drug, and produce periodic safety update reports, which they submit to the drug agencies. The underreporting of adverse drug reactions has been estimated by to be around 90% or more (25), which means that we often lack knowledge about the frequency and seriousness of adverse effects.

When a drug is marketed, there is only limited knowledge about adverse effects, and the perception of the balance between benefit and harm will therefore often change over time. For around half of the drugs, label changes because of serious risks that are only revealed after marketing are introduced (4). The spontaneous reporting system is therefore slow in detecting signals of harm. For this reason, the importance of a transparent cause-effect assessment built on a precautionary principle has been suggested (26, 27). This might be in contradiction to European drug legislation, which is based on a risk management principle (28). When signals of adverse drug reactions have turned up it, is the responsibility of drug authorities to re-assess the risk-benefit relation, and to assess if there is a basis for changes in the market authorization.

Benzodiazepines and abuse potential

In 1967, there were warnings that benzodiazepines were used illicitly, particularly by the youth and in countercultures (29). In 1979, US Congress initiated a hearing about the “Valium scare”, because of the “growing of a very serious public health problem of which American people may not be aware”. As a result of the hearing, the benzodiazepines were regulated by the Drug Enforcement Agency (DEA) and categorised as Schedule IV drugs in the Controlled Substances Act of 1970,

having both medical and abuse potentials (29). WHO recommended in the early 1980s to categorise benzodiazepines as a group as schedule IV under the Psychotropic Convention (30). In 1985, benzodiazepines were categorised as class C drugs in the Misuse of Drugs Act 1971 in UK (31). The schedule (and class C) describe the restrictions to which the drugs are subjected, for example prescription or labelling restrictions, registration of manufacturers and distributors. There are five schedules and IV is the second least restrictive schedule. Most of the benzodiazepines are categorised as schedule IV drugs, only a few are categorised as schedule III drugs. Seven years after their marketing, the abuse potential was recognised, though it took a further 13 years before benzodiazepines were categorised as drugs with abuse potential.

Frequency and severity

In 1996, the UK regulators had the opinion that withdrawal reactions after SSRI discontinuation were rare and not severe. This was challenged by Haddad, Lejoyeux and Young (32) who, in 1998, suggested in an editorial in BMJ that the incidence of withdrawal reactions from SSRIs was 35%, mostly mild to moderate, short-lived, and preventable and simple to treat. Young and Haddad (33) reassessed this in 2000 in a correspondence in The Lancet suggesting an incidence rate between 35% and 78% and with a characteristic SSRI withdrawal syndrome, normally mild and transient, but occasionally of longer duration and with considerable morbidity. These independent assessments were built on data from randomised trials from 1995, 1997 and 1998, but the rapidly increasing risk of withdrawal reactions and increased seriousness was only partly reflected in the communications from the drug authorities. According to the risk management principle, the drug regulators have to await signals about adverse effects from the spontaneous reporting of adverse effects, which suffers from underreporting. It will therefore take time before frequency and seriousness of adverse effects will be recognised and the public can be informed about it.

Semantics

There has been an ongoing controversy whether SSRIs induce withdrawal symptoms or a dependence syndrome. This discussion is connected to the definition of dependence and it is semantic. Several authors, for example Haddad, Lejoyeux & Young (32), emphasize that SSRI discontinuation does not imply drug craving or drug seeking behaviour and express concern that people believe that antidepressants are addictive because of the withdrawal term, which could result in people avoiding treatment. From the patient perspective, the consequences of dependence and

withdrawal syndrome seems to be the same: difficulty stopping the medication because it provokes symptoms.

The role of drug agencies

It can be questioned if the risk management principle is sufficient to protect the public against the risks of drugs. It would seem that the doubt and uncertainty favour the drug companies rather than the patients. John Abraham (34) suggested that drug regulatory decision-making may be understood in the light of a permissive principle, i.e. a tendency to permit a technology on the market, even if it does not meet the standards of efficacy and safety, in contradiction to a precautionary principle. Abraham (7, 27) found that drug regulators tend to weigh the balance of scientific doubts about drug safety in favour of the manufacturer, both pre- and post-marketing.

Malcolm Lader (8) described this conservatism in relation to the benzodiazepines. David Healy (11) showed that the regulatory bodies have only minimal audit functions, as it is the pharmaceutical companies that decide which trials to conduct, and trials are conducted to fit marketing; they are not driven by safety concerns. McGoey (9) described that the UK medicines agency has been mandated over and over again to address the issue of safety of SSRIs, but the consequence was that the authority of drug regulators was strengthened rather than being challenged. She has suggested that ignorance within the drug regulator is being used as an anti-strategy, in order not to reach conclusions on safety.

It is a part of drug approval today that the marketing authorization applicant shall prepare a risk management plan for the specific drug and it shall contain a list of identified and potential risks when using the drug, also the risk of misuse. A risk minimisation program can be required by the drug agency in order to reduce known risks (35). This aims at improving patient safety and is strengthening the risk management model of drug regulation.

Limitations of our study

We limited our searches to documents from FDA, MCA/MHRA, DKMA and EMA. There was consistency between the documents we retrieved. It might be surprising that the search only revealed 23 SSRI documents and 6 benzodiazepine documents. The reasons for this are several. It took time before the adverse effects reached the agenda of the drug regulators and we only searched

for documents that were available on the internet. There are probably documents that are unpublished and inaccessible, but these are not relevant for our study of information provided to the public. The study is based on two therapeutic groups, which makes it difficult to generalise to other drugs, but the problems we identified are also known for other drug groups, as described by Abraham (7, 27). Another potential limitation of our study is that it is based on documents available on the internet. Web-pages are changed over time and information is deleted or moved to other places. However, the identified documents are all dated. Many of the documents about benzodiazepines might never have been available on the internet, as the internet didn't exist at the time. This might have contributed to the restricted number of documents that we were able to identify for the benzodiazepines.

Conclusion

In the light of the precautionary principle and the risk management principle, the results of our study can be understood in two ways. Seen from a precautionary principle, the drug agencies have failed to acknowledge that SSRIs can cause dependence, with reference to the diagnostic disease manuals ICD-10 and DSM-IV, and have prepared conservative estimates with regard to the severity and the number of people affected. In this perspective, changes in the communication from drug regulators to the public about adverse effects happened slowly.

Seen from a risk management principle, the drug agencies have reacted in concordance with the slowly growing knowledge of adverse drug reactions and have sharpened the information to the public over time. However, relying on spontaneous reporting of adverse effects leads to underrecognition and delayed information about the problems. In light of the history of other psychoactive drugs, e.g. benzodiazepines and barbiturates, it is nonetheless surprising that the regulatory bodies have not required studies from the manufacturers that could elucidate the dependence potential of the SSRIs before marketing authorization.

Conflicts of interest: None.

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Table 1: Search strategy

Source	Search words		
www.google.dk	benzodiazepines	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA or DKMA
	SSRI	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA or DKMA
PubMed http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed	Benzodiazepines (Mesh)	Substance withdrawal syndrome (MeSH)	FDA or MHRA or MCA or EMEA
	Serotonin uptake inhibitors (MeSH)	Substance withdrawal syndrome (MeSH)	FDA or MHRA or MCA or EMEA
JAMA http://jama.ama-assn.org/	benzodiazepines	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA
	SSRI	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA
BMJ http://www.bmj.com/	benzodiazepines	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA
	SSRI	Withdrawal syndrome or dependence	FDA or MHRA or MCA or EMEA
FDA http://www.fda.gov/default.htm	benzodiazepines		Withdrawal syndrome or dependence
	SSRI	Serotonin uptake inhibitors (MeSH)	Withdrawal syndrome or dependence
MHRA/MCA http://www.mhra.gov.uk/index.htm	benzodiazepines		Withdrawal syndrome or dependence
	SSRI	Serotonin uptake inhibitors (MeSH)	Withdrawal syndrome or dependence
EMA http://www.ema.europa.eu/	benzodiazepines		Withdrawal syndrome or dependence
	SSRI	Serotonin uptake inhibitors (MeSH)	Withdrawal syndrome or dependence
DKMA http://www.dkma.dk/1024/visUKLSForside.asp?artikelID=728	benzodiazepines		Withdrawal syndrome or dependence
	SSRI	Serotonin uptake inhibitors (MeSH)	Withdrawal syndrome or dependence

Table 2: Results from the document search.

Benzodiazepines

Year	Reference	Citation	Genre
1964	BMJ 1964, 31. October Drugs of addiction	List of substances especial liable to cause drug-dependence: Librium, chlordiaze-poxide	Article in BMJ.
1980	Committee on the Review of Medicines (1980). Systematic review of benzodiazepines. BMJ;280, 910-2.	However, following an extensive review of all available data the committee concluded that, on the present available evidence, the true addiction potential of benzodiazepines was low. The number dependent on benzodiazepines in the UK from 1960 to 1977 has been estimated to be 28 persons.	Systematic review
1980	Cirkulære om lægers ordination af afhængighedsskabende lægemidler [Circular about doctors prescriptions of addictive medicines]. Circular number 97 15.06.1980 Danish National Board of Health	[All mentioned groups of drugs can cause addiction. The risk is greatest for morphine and amphetamine. The doctor shall, when prescribing anxiolytics or hypnotics, take care that the patient only is prescribed what seems reasonable for the treatment.]	Circular – a law text
1980 - 1982	Medical Research Council Headquarters file 1980-82 http://www.benzo.org.uk/amisc/mrc82.pdf	Professor Lader explained that he thought that there was a “iceberg effect” of benzodiazepine dependence. A pronounced withdrawal syndrome showed up as a consistent pattern of physiological changes on withdrawal of the drug. Although dependence occurs	Headquarters file, with letter, minutes, notes. Name of file: Benzodiazepine dependence.

		in only a small proportion of benzodiazepine takers the number of patients involved may be substantial. The risks of dependence could be reduced by more trained prescribing of benzodiazepine.	
1988	Medicines Control Agency, Committee on Safety of Medicines (1988). Benzodiazepines, dependence and withdrawal symptoms. Current problems in Pharmacovigilance, 21, 1-2.	There has been concern for many years regarding benzodiazpine dependence (Br.Med.J,1980:280:910-12). Such dependence is becoming increasingly worrying.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners.
1993	Circular about prescription of addictive drugs. Circular number 110 28/06/1993. Danish National Board of Health.	[Usage in Denmark is above the international average. It is not the intension with these guidelines to question current treatment. They are for short term treatment. For severe, disabling cases.]	Circular – a law text

SSRIs

Year	Reference	Citation	Genre
1993	Medicines Control Agency, Committee on Safety of Medicines (1993). Dystonia and withdrawal symptoms with paroxetine (Seroxat). Current problems in pharmacovigilance 19, February.	We have received 78 reports of symptoms occurring on withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion. Such reactions have been reported more often with paroxetine than with other SSRIs.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners
1996	Price J.S, Waller P.C., Wood S.M, Mackay A.V.P. A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. British Journal Clinical Pharmacology. 1996;42:757-63.	It appears that the reports represent genuine withdrawal reactions, but the low frequency of reporting per thousand prescriptions, together with the published	Scientific paper

		comparative studies suggest that, overall symptoms due to stopping an SSRI are rare. The withdrawal symptoms observed do not appear to be severe.	
1998	Committee on Safety of Medicines subcommittee on pharmacovigilance	However, withdrawal reactions occur with all SSRIs and related antidepressants, although to different extents with each drug, and this is now thought to be a class effect. In the main, these reactions are mild and self-limiting, although more severe reactions have been reported	Minutes
1998	Committee on Safety of Medicines. Summary of the meeting of the Committee on Safety of Medicines Held on Thursday 26 March 1998. http://www.mhra.gov.uk/home/groups/l-cs-el/documents/committeedocument/con003341.pdf	They [the committee] commented that dose escalation and drug seeking behaviour were evident in association with benzodiazepines but that these features were not evident in patients taking SSRIs.	Minutes
2000	European Medicines Agency (1999/2000). EMEA/CPMP/2775/99.	The material provided by the pharmaceutical companies with regard to dependence and withdrawal of SSRIs is of variable quality and	Position paper

		quantity. For the majority of the compounds the studies were not designed to study withdrawal phenomena and lack sufficient observations in the critical period after stopping administration.	
2000	Medicines Control Agency, Committee on Safety of Medicines (2000). Current problems in pharmacovigilance,	In 1993 we alerted prescribers to the possibility of withdrawal reactions occurring with paroxetine. Whilst the withdrawal symptoms reported were generally not serious, there have been isolated reports of more serious symptoms on withdrawal such as severe electric shock sensations, vertigo and manic reactions.	Article in the bulletin sent out from the MCA to doctors, pharmacists, dentists and coroners
2000	EMEA CPMP 2278/00	Some of the SSRIs have been shown to reduce intake of addictive substances like cocaine and ethanol. The interpretation of this aspect is difficult.	
2002	Tonks A. (2002). Withdrawal from paroxetine can be severe, warns FDA. British Medical Journal, 324, 260.	FDA Warning against paroxetine because of the risk of withdrawal symptoms.	News in BMJ
2002	MHRA response to Panorama programme on Seroxat	All SSRIs may be associated with withdrawal reactions on	Safety message

		stopping but they are not drugs of dependence.	
2002	Ad Hoc Expert Meeting 21 November on the safety of SSRIs	The Group did not consider that withdrawal reactions and dependence were synonymous. The Group did not consider that SSRIs caused dependence.	Minutes
2003	DKMA Danish Medicines Agency (19 June 2003). Summary of Product Characteristics for Serorex (paroxetine) http://www.produktresume.dk/docushare/dsweb/Get/Document-14813/Serorex%2C+filmovertrukne+tabletter+20+mg.doc	[Though abstinence reactions can occur at discontinuation, all preclinical and clinical data do not indicate that SSRIs cause dependence]	SPC
2003	DKMA Lægemiddelstyrelsen (2003). Antidepressive midler under vurdering (Antidepressants under assessment).	[It is important to emphasize that it is about discontinuation symptoms and not actual dependence to the drugs.]	Article to the public because of media referring to problems with the antidepressants.
2003	Meeting of the CSM Expert group on the safety of SSRIs held on Tuesday 22nd July.	The group commented that it was a challenge to disseminate the information [about withdrawal reaction] in such a way that informed patients of the risks but did not stop them taking the medication.	Minutes
2003	Committee on Safety of Medicines	No strong evidence has been identified to suggest that SSRIs cause other features of dependence.	Minutes
2003	WHO Expert Committee on drug dependence WHO Techical Report series no 915. Thirty third report. WHO Geneve.	Three SSRIs are among the 30 highest-ranking drugs in the list of	Technical report

		drugs for which drug dependence has ever been reported to the Uppsala Monitoring Centre database.	
2003	Meeting 16 September CSM and Expert group on Safety of SSRIs	The group expressed concern about the lack of data on the long-tern effect of SSRIs and recommended that further research on this area was required.	Minutes
2003	Committee on Safety of Medicines and Expert Group on Safety of SSRIs. Minutes of the meeting held Tuesday 25 November 2003. http://www.mhra.gov.uk/home/groups/pl-p/documents/committeedocument/con003487.pdf	Professor Drummond explained that he had considered to what extent the SSRIs meet the ICD-10 and DSM-IV definitions of dependence and has concluded that the extent to which SSRIs meet the criteria is much less than with other typically dependence producing drugs.	Minutes
2003	Interim report of the Committee on Safety of Medicines´ Expert Working Group on Selective Serotonin Reuptake Inhibitors September 2003	Two areas of continual concern …. and withdrawal reactions on stopping SSRIs.	Report
2003	WHO Pharmaceutical Newsletter 2003; no 1. Drugs of abuse: Problems of data collection, definitions and liability assessment.	However, such a conclusion may only be drawn after a careful review of the significant number of "drug dependence" reports for SSRIs received by the ADR monitoring system and, not on the basis	Newsletter

		of the terminology discussion that withdrawal reactions by themselves are insufficient to imply dependence.	
2004	Committee on Safety of medicines URL:http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019472.pdf	There is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome according to internationally accepted criteria (either DSM-IV or ICD-10)	Scientific report
2004	Committee on Safety of Medicines, Expert Group on Safety of SSRIs. Tuesday 9 November 2004.	A proportion of SSRI withdrawal reactions are severe and disabling to the individual.	Minutes
2005	Danish Medicines Agency (20 June 2005). Summary of Product Characteristics for Seroxat (paroxetine). http://www.produktresume.dk/docushare/dsweb/Get/Document-21876/Seroxat%2C+filmovertrukne+tabletter+20+mg+og+30+mg.doc	[Occurrence of discontinuation symptoms does not imply that the drug is addictive or cause dependence.]	Summary of Product Characteristics
2005	European medicines Agency Doc. Ref. EMEA/CHMP/PHVWP /397128/2005	Generally these events[withdrawal symptoms] are mild to moderate and are self-limiting, however in some patients they may be severe and/or prolonged.	Core SPC Wording for SSRIs