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A review of the Danish National Drug Directory: Who provides the data for the register?

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Abstract: We have analyzed the Danish national drug directory (Medicine.dk) and found that it provides the information from industrial drug trials instead of the more objective and reliable information on the drugs provided by meta-analyses made by researchers independent of the pharmaceutical industry, like the Cochrane collaboration. The consequence of this is a strong bias, as a large fraction of the drugs are presented more positive and less harmful than they actually are. Whole classes of drugs that in independent meta-analyses have been found to be of little clinical value, or even harmful, are still listed in the national drug directories as beneficial drugs, i.e. anti-cancer chemotherapy, the anti-depressive drugs, and the anti-psychotic drugs. To solve this serious problem of misguidance, we have identified the core principles for rational listening of data regarding positive and negative effects of the pharmaceutical drugs. An outline of a standard list of positive and negative drug effects is suggested. Information on each drug should be provided with due regard to dose, indication of use, all clinically relevant outcomes, method of drug study used for documentation, including placebo type, and the quality of the study. We recommend the use of *Number Needed to Treat* (NNT) and *Number Needed to Harm* (NNH) for each single situation. When more objective and reliable data exist, they should be preferred rather than more doubtful data from studies of lower quality. We warn physicians and patients that the existing drug directory is strongly biased and not a reliable source of information.

Keywords: National Drug Directory, bias, clinically relevant outcomes, horizontal risk measures, vertical risk measures, NNT, NNH, Cochrane Meta-analysis

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INTRODUCTION

In Denmark most physicians and patients are treated according to the Danish Drug Directory (Medicin.dk) (1). We observed that the information on pharmaceutical drugs in this directory is in line with the pharmaceutical industry documentation of its products and often in conflict with data

from independent research on drug efficacy and harm made by researchers in the Cochrane movement and other research projects making meta-analyses of the positive and negative effects of the drugs.

This situation is highly problematic. First the Danish law on pharmaceutical drugs (2) makes it clear that the pharmaceutical companies are obliged to inform the Danish Medicines Agency about all new studies that contain new information about the relationship between benefit and harm of the drugs. Secondly, the physician and patient has to choose between a medical treatment with drugs and without drugs, as non-drug treatments are becoming increasingly popular in Denmark, with many chronic patients selecting alternative therapy (3). Without correct information, the choice of the patient can never be rational.

We are aware of the financial interests in the pharmaceutical drugs, and we understand why biases are so often introduced when the pharmaceutical industry is documenting its own products. This knowledge makes it important that we ensure that the correct data are delivered to physicians and patients.

THE LAW ON PHARMACEUTICAL DRUGS IN DENMARK

In Denmark, the Law on Pharmaceutical Drugs (2) regulates the sale and marketing of drugs. The text begins with the purpose of the law: §1. The purpose of the law is to secure, that the citizens "*1) have access to safe and effective pharmaceutical drugs of high quality", 2) has access to objective and adequate information about the pharmaceutical drugs and 3) is being protected from misleading commercials for pharmaceutical drugs and other illegal marketing of pharmaceutical drugs*."

The law informs when a drug cannot be on the market: §12. The Medicines Agency declines a marketing permit to a pharmaceutical drug, if: 1) the relationship between benefits and risks is un-favorable (Cmp. §2), 2) there is no therapeutic effect, or the therapeutic effect has not been sufficiently documented by the applicant for the permit, or 3) the medicine has not the specified qualitative or quantitative composition." §25 notify that the holder of a marketing permit must inform the Medicines Agency about any significant new information regarding the relation between benefits and risks of a drug.

THE EFFICACY AND HARM OF CLASSIC NON-DRUG MEDICINE

During the last three decades, sufficient research has been conducted to establish the number of patients needed to be treated for one to be cured (*Number Needed to Treat*, NNT) and the number of patients needed to be treated for one to be harmed (*Number Needed to Harm*, NNH) with non-drug holistic and complementary medicine (CAM).

The classic type of non-drug medicine, the holistic Hippocratic character medicine, was until recently in general use all over Europe and had been so for more than 2000 years (4). In three reviews (5-7) we estimated the general NNTs and NNHs for the most efficient non-drug medicine and found these numbers to be 2 and 64,000 respectively (NNT = 1-3 for the outcome "cured" and NNH = 64,000 for the only significant side effect found, which was brief reactive psychosis).

Research has documented the clinical effect of holistic medical treatment for a long list of clinical conditions (see table 1). The classical medicine seems to help about 50% of its patients, which is considered

"effective" medicine; less than one patient in a thousand is harmed, which is considered "safe" medicine.

NNT, NNH AND THERAPEUTIC VALUE OF DRUGS

Since 1960, biomedical drugs have been developed for a long list of diseases and clinical conditions, of which many are out of clinical reach with non-drug medicine, like antibiotics for syphilis or meningitis. The general NNTs and NNHs of the pharmaceutical drugs has been established to be 20 and 3 respectively (NNT = 20 for the outcome "improved" (5), NNH = 3 for most common adverse effect); see reference (6) for review.

Although most drugs have only one important effect, there are often several adverse effects, making the total likelihood to get one significant adverse reaction larger than the NNH for the most common adverse effect of the drug (NNT_{total} is often about 3 times the NNH of the most common adverse effect, or about NNH_{total} = 1, for the treatment of most serious physical and mental diseases) (5-14). Recent reviews and Cochrane meta-analyses have documented a very problematic relationship between positive and negative effects for large groups of drugs, like the anti-depressant and the anti-psychotic drugs (13,14). We know from this that many drugs have problems in relation to the law as the drugs are not effective (only 5% of the patients are helped with most drugs) and the benefits are often much smaller than the harm. Expressed in NNT and NNH, the therapeutic value NNT/NNH_{total} is less than one ($NNT/NNH_{total}<1$).

During the 1970s and 1980s, there was strong optimism about the pharmaceutical drugs, which in some European countries like Denmark has led to the nationalized medicine almost exclusively using pharmaceutical drugs; the use of which has been guided by national pharmaceutical drug directories. Unfortunately, biomedical drugs have failed to be curative for many diseases, and 40 years after the introduction of nationalized biomedicine in Denmark, every second Dane has a chronic disorder not cured by the drugs (13). This situation has lead to renewed interest for non-drug medicine, with an exponential development of the interest from about 10% of the population using complementary and alternative (CAM) and holistic medicine in 1990 to 20% using them in 2000 (3), with an estimated 40% of the population using it today. Basically all chronic patients not helped much by pharmaceutical drugs go for classical non-drug medicine with talk-touch therapy. Unfortunately, most of this is rather inefficient CAM-therapy [like flower medicine (16)] and not the classical, holistic mind-body medicine, which is now rarely provided by the physicians as this method is no longer included in the curriculum of Danish medical schools. In contrast to this, many American universities include non-drug mind-body medicine in their curriculum (17).

The law itself, as well as the explosive growth in interest for non-drug treatments, makes it mandatory that the efficacy and harm from pharmaceutical medicine are known to the physicians, the patients, and the Medicines Agency.

The Danish Drug Directory (Medicin.dk) does not give the necessary data to evaluate the therapeutic value (NNT/NNH_{total}) of a drug. Today these national directories are constructed in such a way that it is impossible to identify the NNTs and NNHs for the treatment of a specific clinical condition with a drug; therefore nobody can know if a drug is of therapeutic value or if a non-drug treatment is the most efficient. The reason for this regretful state of affairs

Table 1. *Estimated NNT-numbers of the CAM treatments of physical, mental, existential and sexual health issues and working disability (mostly based on clinical studies using chronic patients as their own control, see (6))*

CAM for physical health	
Subjectively poor physical health	NNT=3 (18,19,40)
Coronary heart disease	NNT=2-4 (66,67)
Cancer (QOL, survival)	NNT=2,7 (68,69,70)
Chronic pain	NNT=2-3 (21,40)
CAM for mental health	
Subjectively poor mental health	NNT=2-3 (18-21)
Schizophrenia	NNT=3-5 (23,34)
Major depression	NNT=2-3 (59-61)
Anorexia Nervosa	NNT=3 (59-61)
Anxiety	NNT=3 (59-61)
Social phobia	NNT=3 (59-61)
CAM for sexual dysfunctions	
Subjectively poor sexual functioning	NNT=2 (42,62,63,64)
Male erectile dysfunction	NNT=2 (63)
Female orgasmic dysfunction	NNT=1 (64)
Female lack of desire	NNT=2 (62,63)
Female dyspareunia	NNT=2 (27,45,63)
Vaginismus	NNT=2 (27,63)
Vulvodynia	NNT=2 (27,44,63)
Infertility (close ovarian tubes)	NNT=6 (58)
CAM for psychological and existential problems	
Subjectively poor quality of life	NNT=2 (36,37,43)
Sense of coherence	NNT=2-3 (36,37)
Suicidal prevention (with decisions)	NNT=1 (30)
Low self esteem	NNT=2 (44)
CAM for low working ability	
Subjectively poor working ability	NNT=2 (39)

is not clear at all. One reason is that the law for some strange reason does not compel pharmaceutical companies to inform the Medicines Agency about the NNT and the NNH and NNH_{total} for the drugs, which is very strange indeed, as the values of NNT and NNH_{total} are needed to estimate the therapeutic value of a drug. Without these figures a rational evaluation of the therapeutic effect cannot be made.

One can argue that the fraction NNT/ NNH_{total} is not a clear cut scientific expression of therapeutic value. It is known that this is not true as the pharmaceutical industry for many years has made such measures for the positive effects more sensitive in the RCTs (randomized clinical trials), going from global measures of "quality of life" and "cured" to "symptoms improved" and further to the present day

Table 2: *Evidence Level 1-10 (quality) of drug trials. The reliability of the trial varies significantly with the level of analysis (RCT, review of RCTs, meta-analysis of RCTs, national study, cohort study) and the level of independency from the pharmaceutical industry. (1 is best and most reliable quality, 10 worst and least reliable) (Comp. 76,77)*

1.	Cohort studies of long term positive and negative effects of pharmaceutical drugs on the different categories of patients made by independent researchers at independent research centers
2.	Data from national studies using central registers made by independent researchers at independent research centers
3.	Meta-analyses of meta-analyses of RCTs made by independent researchers at independent research centers (studies including several meta-analysis)
4.	Reviews of meta-analyses of RCTs made by independent researchers at independent research centers (including several meta-analysis)
5.	Meta-analyses made by independent researchers at independent research centers
6.	Reviews of RCTs made by independent researchers at independent research centers
7.	Cohort studies of long term positive and negative effects of pharmaceutical drugs on the different categories of patients made by physicians, statisticians and other experts paid or in any other ways supported by the pharmaceutical industry
8.	Data from national studies using central registers made by physicians, statisticians and other experts paid or in any other ways supported by the pharmaceutical industry
9.	Meta-analysis of RCTs made by physicians, statisticians and other experts paid or in any other ways supported by the pharmaceutical industry
10.	RCTs sponsored by pharmaceutical companies or foundations and national agencies with members in some way supported by the pharmaceutical industry, or with members from academic institutions in some way supported by pharmaceutical companies.

use of measures of "symptoms somewhat improved"—all done to improve the NNTs from around 100 around 1950 to around 20 today. At the same time the measures for adverse effects have been made less and less sensitive, removing all global expressions of harm from the RCTs, making the NNHs larger. All this indicates that the fraction NNT/NNH_{total} is biased in favor of the pharmaceutical industry's products, but it is still the best measure we have—and when it comes down to it, the only scientific measure.

LISTING POSITIVE/NEGATIVE EFFECTS

A serious problem in providing accurate and reliable information about the effects of pharmaceutical drugs is the varying quality of the documentation of drug efficacy and harm. We therefore suggest a 10-step system for grading the evidence levels of the drug trials (see table 2).

The pharmaceutical companies own documentation is known to be biased (71), which explains the significant difference between the documented efficacy of the drugs in industrial drug trials (RCTs) and in meta-analysis made by independent researchers at independent research institutions (72). The Cochrane meta-analysis finds systematically less effect and more harm from the pharmaceutical drugs than the pharmaceutical industry does, when it documents its own products. Well-known examples include the negative effects of chemotherapy on quality of life and survival found by Ulrich Abel (10-12) and the lack of improvement of the mentally ill patients' mental state with anti-psychotic or anti-depressant drugs found in

Cochrane reviews (13,14). The indisputable higher qualities of independent meta-analysis makes it of utmost importance that the results from such studies are used in national drug directories, when they exist at all, rather than the data from the pharmaceutical industries.

Another problem is that active drugs often can be felt by the patient, breaking the blindness of the study and introducing a severe error due to the active placebo effect (73). It has been documented that the positive effects of the anti-depressive drugs found in drug trials with normal (passive) placebo disappeared when active placebo was used (14). If drug trials with active placebo exist, then the results from such trials must be reported instead of the results from drug trials using the incorrect placebo type.

There has been a strong tendency to not document the adverse effects of new drugs sufficiently, making the new drugs seem more efficient that the older drugs, with this tendency disappearing as times goes by and more and more adverse effects are registered, as we have seen with the anti-psychotic drugs (13). This is a severe problem as both physicians and patients are misled to believe that the new drugs are better, making these drugs used more often despite a far higher price and no true advantage. To avoid this problem it is important that global outcome measures of quality of life and self-assessed physical and mental health be included in all future drug trials with the validated QOL1 and QOL5 that has been developed for this purpose (74). If a drug fails to improve global quality of life and either self-assessed physical or mental health, then that drug should not be approved because then the adverse effects are greater than the beneficial effects.

A problematic tendency is to report the positive and the negative outcomes differently. It has been shown that patients, physicians and politicians are less positive to treatments when they know the NNT numbers (75). There has been a tendency to hide the NNT numbers and to replace them with horizontal risk measures, which gives the impression that the positive effect is for every patient, despite this obviously not being the case. At the same time, adverse effects are often reported vertical risk measures like NNH. The combination of horizontal effect measures for the positive effects with vertical effect measures for the negative makes the drugs look more beneficial and less harmful than they really are. Not using the same measures for positive and negative effects makes it impossible to evaluate the relation between positive and negative effects, thus seriously violating the intention of the Law on pharmaceutical drugs.

HOW TO REPORT EFFICACY AND HARM

Many problems follow from the inaccurate listing of positive and negative effects; a common problem is known as “dose-response-bias” where the dose of drug used for measuring the positive outcomes differs significantly from the dose of drugs used for measuring the negative outcomes (71). The only way to ensure that such a bias is not introduced is to place positive and negative effects in a list under the same dose.

Another problem is the confusion of outcomes, as when reduction of unwanted behavior (i.e. “hallucinatory behavior”) is confused with improvement of mental health (the outcome “mental state”). Such confusions are common, making it necessary to strictly list all positive outcomes and the NNT for each.

If an industry-independent measure of NNT and NNH (Evidence level 1-6) exists,

then these should replace the NNTs and NNHs provided by the pharmaceutical industry and its collaborators. If there are NNT-numbers and NNH-numbers from drug trials using active placebo, these should replace the NNTs and NNHs from studies using passive placebo. If there are several HHTs and NNHs from more than one study in the high evidence group level 1-6, then all these numbers should be provided; if there are several studies in the low evidence group 7-10, then all these should be provided.

In general, the patients and his/her physician should trust the higher NNT and the lower NNH as massive commercial interests induce bias in almost every single drug trial. The independent meta-analysis is still often based on the industrial RCTs, taking all the bias before statistical analysis with them into the meta-analysis. It is also important to be aware of the inherent problems of the RCT-test itself not to be over-optimistic of the treatment results from the pharmaceutical drugs (72).

It is of crucial importance that the drug directories follow the standard for medical science, with a complete and open reference system. As it is now, references are not included in the national drug directories (neither in the book (1), nor on the homepage (78), nor on any side linked to the homepage) making it very difficult to realize what the source of the data really is; only by comparison of the actual data can you see that they are not from the independent meta-analysis, as they should be, but from other sources strongly biased in favor of the pharmaceutical drugs.

The Danish Drug Directory is based on the approved industrial product resumes delivered by the Danish Medicines Agency (Lægemiddelstyrelsen). The procedure for these resumes is that the pharmaceutical industry makes a draft, which is then rejected/approved by the Danish Medicines Agency (2,79). Only the pharmaceutical industry has the references and the Danish Medicines Agency refers people interested in the references back to the pharmaceutical companies (79). Based on these considerations, we recommend that national pharmaceutical drug directories be made as follows. For each drug, the following data regarding the positive and negative effects must be listed. Table 3 gives an example of how such a table might be structured.

Positive effect(s):

- One table must be made for each specific treatment indication and for each recommended dose.
- For each dose, and each indication the table must include: The NNT for each outcome (i.e. “20% improvement”, “50% improvement”, “cured”
- For each NNT: information on the term used for the test: a) short term (0-6 month), b) intermediate (6-12 month) and c) long term treatment (12-60 month).
- For each NNT: information on the test method: a) RCT with active placebo, b) RCT with passive placebo, c) RCT with no treatment, , d) Other test.
- For each specific treatment indication and for each recommended dose the improvement on global quality of life and self-rated mental and physical health must be listed.
- For each NNT the quality of the study (Evidence Level 1-10, in accordance with table 2)

Table 3. *Structure of table for listing the positive and negative effects and therapeutic value of pharmaceutical drugs*

Drug A, dose α				
A α 1. Indication: Disease D1				
		Short term	**Medium term**	**Long term**
Positive effects (Benefit)				
A α 1-B(1)				
Outcome 1: XXX.	NNT	X	X	X
Method:		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(1,2,3…)	(6,7,8…)	(12,13,14…)
A α 1-B(2)				
Outcome 2: XXX.	NNT	X	X	X
Method:		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(21,22,23…)	(26,27,28…)	(32,33,34…)
ETC				
Negative effects (Harm)				
A α 1-H(1)				
Adverse effect 1: XXX.	NNH	X	X	X
Method: :		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(41,42,43)	(46,47,48)	(52,53,54)
A α 1-H(2)				
Adverse effect 2: XXX.	NNH	X	X	X
Method: :		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(61,62,63…)	(66,67,68…)	(72,73,74…)
A α 1-H(3)				
Adverse effect 3: XXX.	NNH	X	X	X
Method: :		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(81,82,83…)	(86,87,88…)	(92,93,94…)
A α 1-H (Death)				
Death	NNH	X	X	X
Method: :		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(121,122,123…)	(126,127,128…)	(132,133,134…)
A α 1-H (total)				
Total harm	NNH_{total}	X	X	X
Method: :		a/b/c/d	a/b/c/d	a/b/c/d
Evidence level (1-10)		N	N	N
Reference		(221,222,223…)	(226,227,228…)	(232,233,234…)

Table 3. *Structure of table for listing the positive and negative effects and therapeutic value of pharmaceutical drugs (continued)*

Therapeutic value (Benefit/Harm)
Estimated therapeutic value for the treatment of disease 1 with drug A, dose α:

	Short term	**Medium term**	**Long term**
Therapeutic value (NNT/NNH_{total})	X	X	X

A α 2. Indication: Disease D2

	Short term	**Medium term**	**Long term**

ETC

A α 3. Indication: Disease D3

	Short term	**Medium term**	**Long term**

ETC

Drug A, dose β
ETC
Drug A, dose μ
ETC

Drug B, dose α
ETC

REFERENCES

- Only clinically relevant outcomes should be listed. If a biomedical parameter or "diseases marker" is improved, and there is no data on the improvement on the patients' health, such data should not be listed in the national drug directory, as it is most likely that the patients are not benefiting from the intervention (78). A 3%, 5%, or 10% improvement is clinically irrelevant and should not be included in the list of outcomes. Horizontal risk measures are normally used when the improvement has only this size and they therefore mislead patients and physicians to believe that a clinically insignificant effect like a 3% improvement has clinical significance and should therefore be avoided.
- If the information is not available, then information on the "missing info" must be found in the table.

Negative effects

- One table of adverse effects and events must be made for each specific treatment indication and for each recommended dose.
- For each specific treatment indication and for each recommended dose the negative impact on global quality of life and self-rated mental and physical health must be listed.
- For each dose and each indication, the table must include: The NNH for each adverse effect and each adverse event,

including suicide and sudden unexplained death, and the total likelihood for getting an adverse effect/event (NNH_{total}) (1).

- For each NNH: information on the term used for the test: (a) short term (0-6 month), (b) intermediate (6-12 month), and (c) long term treatment (12-60 month).
- For each NNH: information on the test method: (a) RCT with active placebo, (b) RCT with passive placebo, (c) RCT with no treatment, (d) Other test.
- If the information is not available, then the information on the "missing info" must be found in the table.

Therapeutic value

The therapeutic value is finally calculated as NNT/NNH^{total}.

DISCUSSION

We analyzed the Danish National Drug Directory (Medicine.dk) (1) and found that it does not follow the above mentioned simple principles for listing positive and negative effects in national drug directories. Whole classes of drugs that in independent meta-analyses have been found to be of little clinical value, or even directly harmful, are still listed in the national drug directories as beneficial drugs, i.e. anti-cancer chemotherapy, anti-depressive drugs, and anti-psychotic drugs (10,13,14). We have based on this estimated that at least half the listed drugs are presented as more efficient and less harmful than they are found to be in Cochrane meta-analyses and other more objective studies compared with the documentation provided by the pharmaceutical industry's own drug trials ("sponsored trials").

It seems that strong commercial and political interests have influenced how the drugs are presented in the national directories of pharmaceutical drugs. The standard procedure is that the pharmaceutical industry provides the draft of the product resumes, which then is used by the National Danish Drug Directory to inform physicians and patients. Often the best quality of data from the meta-analyses made by independent researchers, which gives a much more nuanced picture of the effects than the often overwhelmingly positive results from the industrial drug trials, are ignored in the drug directories. Taking the data directly from the pharmaceutical industry will most likely introduce a strong bias in favor of the drugs (71).

As a general rule, researchers have noticed that the positive effects are smaller and the harmful effects more severe in the independent drug trials than in the documentation provided by the pharmaceutical industry and its collaborators (71). In meta-analysis, the positive effects of many types of drugs, i.e. anti-cancer chemotherapy (10-12), anti-depressant (14) and antipsychotic drugs (13), have often been found to be almost non-existent, whereas the negative effects have been severe or even fatal. Many drugs have been found to reduce the patients' quality of life and to shorten life in independent drug trials.

We have also found that different measures are used for positive and negative effects of the drugs, making it look like the drugs help every patient and only harm a few. This practice induces a strong bias in favor of the drugs and should be stopped.

It is of the utmost importance that the most reliable and objective information it brought to the physicians and the patients, but we have noticed that this is not the case in Denmark and many other countries. It seems that the pharmaceutical industry has been able to influence the decision making process on product information and presentation of their data, to such an extent

that the national drug directories are not a reliable source of information on pharmaceutical drugs.

To solve this problem, we suggest that the information on the positive and negative effects of the drugs listed in national drug directories in the future follow a rigid scheme. Only in this way can we avoid the introduction of bias in the drug directories, leading to the extremely problematic listing of harmful drugs as useful medicine, and the most problematic bias from the use of different measures for positive and negative effects, as mentioned above.

We estimate that about 10% of the drugs on the market today would be withdrawn if high-quality studies were used instead of industrial studies. These drugs are only harmful to the patients and must be seen as a major health risk-factor on a national scale. We estimate that 250,000 Danes or 5% of the total population are taking drugs that are only harmful and not beneficial, a large fraction of which will get more or less significant adverse effects and adverse events, some of which are likely to be fatal.

Many chronic patients, who are not helped much by drugs, are interested in holistic medical treatment, and the number has been increasing the later decades; these patients need to know the NNTs and NNHs of all treatment alternatives to make a rational decision of which treatment to choose. Only the NNT and NNH numbers can give the patients comparable information about the two very different types of treatment of biomedicine and holistic medicine. The horizontal measures for positive outcomes, which are the only measures provided today in the national Danish drug directory, do not provide useful information for such a comparison and in general, horizontal measures stating that there is a small value for most patients from the treatment with a drug (small for all) is misleading.

The lack of clear information on the NNTs and NNHs of the drugs in the national directories make the patients make choices of crucial importance for their life based on guessing instead of based on facts, which is highly regrettable. Many patients today are not getting the optimal treatment because of lack of information, and many patients are misled to use drugs that in high-quality meta-analysis have been shown to only have harmful effects.

CONCLUSION

Today there are several sources of data on pharmaceutical drugs; some are provided by the pharmaceutical industry, often in studies of poor quality (71,80), whereas others are provided by independent researcher in high quality meta-analyses. We have, in a number of concrete cases, found that data from the high-quality studies have not been used to in the drug directory; instead this has been based directly on information provided by the pharmaceutical companies. As a result, the information on positive and negative effects (including NNTs and NNHs) are incorrect for large groups of pharmaceutical drugs in the national drug directory Medicin.dk (78).

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REFERENCES

1. Pedersen C, Bjerrum L, Dalhoff KP, Friis H, Hendel J. Medicin.dk 2010. København: Informatum, 2010. [Danish]
2. Lov om lægemidler med noter og stikordsregister, 2. Udg. Lov nr. 1180 af 12. December 2005, som ændret ved lov nr. 538 af 8. Juni 2006 og lov nr 1557 af 20 december 2006 samt ændring ved lov nr 534 af 17. Juni 2008. Copenhagen:, Danish Medicines Agency, 2010.
3. Danish Parliament. Report from the Technology Council on alternative treatment. Christiansborg: Danish Parliament, 19 March 2002. [Danish]
4. Jones WHS. Hippocrates, Vol. I–IV. London: William Heinemann, 1923-1931.
5. Smith R. The drugs don't work. BMJ 2003;327:0-h.
6. Ventegodt S, Andersen NJ, Kandel I, Merrick J. Effect, side effects and adverse events of non-pharmaceutical medicine. A review. Int J Disabil Hum Dev 2009;8(3):227-35.
7. Ventegodt S, Omar HA, Merrick J. Quality of life as medicine: Interventions that induce salutogenesis. A review of the literature. Soc Indicator Res Online ISSN 0303-8300, 21 April 2010.
8. Ventegodt S, Merrick J. A review of side effects and adverse events of non-drug medicine (non-pharmaceutical CAM): Psychotherapy, mind-body medicine and clinical holistic medicine. J Compl Integr Medicine 2009;6(1):16.
9. Ventegodt S, Flensborg-Madsen T, Andersen NJ, Svanberg BØ, Struve F, Merrick J. Therapeutic value of antipsychotic drugs: A critical analysis of Cochrane meta-analyses of the therapeutic value of anti-psychotic drugs. J Altern Med Res 2010;2(3), in press.
10. Abel U. Chemotherapy of advanced epithelial cancer—a critical review. Biomed Pharmacother 1992;46:439-52.
11. Abel U. [Chemotherapy of advanced epithelial cancer.] Stuttgart: Hippokrates Verlag, 1990. [German]
12. Abel U. [Chemotherapie fortgeschrittener Karzi-nome. Eine kritische Bestandsaufnahme.] Berlin: Hippokrates, 1995. [German]
13. Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia. Cochrane Database Syst Rev 2007;(2):CD000284.
14. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database Syst Rev 2004;(1):CD003012.
15. Kjøller M, Juel K, Kamper-Jørgensen F. [Folkesundhedsrapporten Danmark 2007]. Copenhagen: Statens Inst Folkesundhed, 2007. [Danish]
16. Susan M. Review shows no evidence that individualised herbal treatments are effective. BMJ 2007;335:743.
17. Wetzel MS, Eisenberg DM, Kaptchuk TJ. Courses involving complementary and alternative medicine at US medical schools. JAMA 1998;280(9): 784-7.
18. Harrington A. The cure within: a history of mind-body medicine. New York: WW Norton, 2008.

19. Goleman D, Gurin J, Connellan H. Mind, body medicine: How to use your mind for better health. New York: Consumer Reports Books, 1993.
20. Sobel DS. Mind matters, money matters: The cost-effectiveness of mind/ body medicine. JAMA 2000; 284(13):1704.
21. Sobel DS. The cost-effectiveness of mind-body medicine interventions. In: Mayer EA, Saber CB, eds. The biological basis for mind body interactions. Progr Brain Res 2000;122: 393-412.
22. Koemeda-Lutz M, Kaschke M, Revenstorf D, Scherrmann T, Weiss H, Soeder U. [Evaluation of the effectiveness of body-psychotherapy in out-patient settings (EEBP)] Psychother Psychosom Med Psychol 2006;56(12):480-7. [German]
23. Röhricht F, Papadopoulos N, Suzuki I, Priebe S. Ego-pathology, body experience, and body psychotherapy in chronic schizophrenia. Psychol Psychother 2009;82(Pt 1):19-30.
24. Broderick JE. Mind-body medicine in rheumatologic disease. Rheum Dis Clin North Am 2000;26(1):161-76.
25. Dreher H. Mind-body interventions for surgery: Evidence and exigency. Adv Mind-Body Med 1998;14:207-22.
26. Barrows KA, Jacobs BP. Mind-body medicine. An introduction and review of the literature. Med Clin North Am 2002;86(1):11-31.
27. Bø K, Berghmans B, Mørkved S, Van Kampen, M. Evidence-based physical physical therapy for the pelvic floor. Bridging science and clinical practice. New York: Elsevier Butterworth Heinemann, 2007.
28. Vickers A, Zollman C. ABC of complementary medicine. Massage therapies. BMJ 1999;319(7219):1254-7.
29. Allmer C, Ventegodt S, Kandel I, Merrick J. Positive effects, side effects and adverse events of clinical holistic medicine. A review of Gerda Boyesen's nonpharmaceutical mind-body medicine (biodynamic body-psychotherapy) at two centres in United Kingdom and Germany. Int J Adolesc Med Health 2009;21(3):281-97.
30. Ventegodt S, Kandel I, Merrick J. Positive effects, side effects and negative events of intensive, clinical, holistic therapy. A review of the program "meet yourself" characterized by intensive body-psychotherapy combined with mindfulness meditation at Mullingstorp in Sweden. J Altern Med Res 2009;1(3):275-86.
31. Ventegodt S, Kandel I, Merrick J. First do no harm: an analysis of the risk aspects and side effects of clinical holistic medicine compared with standard psychiatric biomedical treatment. ScientificWorldJournal 2007;7: 1810-20.
32. Susan M. Review shows no evidence that individualised herbal treatments are effective. BMJ 2007;335:743.
33. Ventegodt S, Merrick J. What is the most efficient way to improve health: Changing your lifestyle or improving your quality of life? In: Kinger LV, ed. Focus on lifestyle and health research. New York: Nova Science, 2005;1-22.
34. Knight RP. Preface. In: Searles HF. Collected papers on Schizophrenia. Madison, CT: Int Univ Press, 1965:15-8.
35. Astin JA, Shapiro SL, Eisenberg DM, Forys KL. Mind-body medicine: State of the science. Implications for practice. J Am Board Fam Pract 2003; 16:131-47.
36. Fernros L, Furhoff AK, Wändell PE. Improving quality of life using compound mind-body therapies:

evaluation of a course intervention with body movement and breath therapy, guided imagery, chakra experiencing and mindfulness meditation. Qual Life Res 2008;17(3):367-76.
37. Fernros, L. Improving quality of life with body-mind therapies. The evaluation of a course intervention for personal self-awareness and development. Dissertation, Stockholm: Karolinska Institutet, 2009. Available at: http://diss.kib.ki.se/2009/978-91-7409-356-8/. Accessed 01 Mar 2009.
38. Ventegodt S, Kandel I, Merrick J. A study in experienced chronic pain in the holistic medicin clinic using mindful psychodynamic short time psychotherapy complemted with bodywork. J Pain Manage 2008;1(1):55-62.
39. Ventegodt S, Andersen NJ, Merrick J. Clinical holistic medicine in the recovery of working ability. A study using Antonovsky salutogenesis. Int J Disabil Hum Dev 2008;7(2):219-22
40. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Clinical holistic medicine (mindful, short-term psychodynamic psychotherapy complemented with bodywork) in the treatment of experienced physical illness and chronic pain. Scientific WorldJournal 2007;7:310-6.
41. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Clinical holistic medicine (mindful, short-term psychodynamic psychotherapy complemented with bodywork) in the treatment of experienced mental illness. ScientificWorldJournal 2007; 7:306-9.
42. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Clinical holistic medicine (mindful, short-term psychodynamic psychotherapy complemented with bodywork) in the treatment of experienced impaired sexual functioning. Scientific WorldJournal 2007;7:324-9.
43. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Clinical holistic medicine (mindful, short-term psychodynamic psychotherapy complemented with bodywork) improves quality of life, health, and ability by induction of Antonovsky-salutogenesis. ScientificWorldJournal 2007;7:317-23.
44. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Self-reported low self-esteem. Intervention and follow-up in a clinical setting. ScientificWorldJournal 2007;7: 299-305.
45. Ventegodt S, Clausen B, Merrick J. Clinical holistic medicine: pilot study on the effect of vaginal acupressure (Hippocratic pelvic massage). Scientific WorldJournal 2006;6:2100-16.
46. Grof S. Realms of the human unconscious: Observations from LSD research. New York: Viking Press, 1975.
47. Grof S. LSD psychotherapy: Exploring the frontiers of the hidden mind. Pomona, CA: Hunter House, 1980.
48. Grof S. Beyond the brain: Birth death and transcendence in psychotherapy. Albany, NY: State Univ New York Press, 1985.
49. Grof S. The holotropic mind: The three levels of human consciousness and how they shape our lives. San Francisco: Harper Collins, 1992.
50. Grof S. The cosmic game: Explorations of the frontiers of human consciousness. Albany, NY. State Univ New York Press, 1998.
51. Grof S. Psychology of the future: Lessons from modern consciousness research. Albany, NY: State Univ New York Press, 2000.

52. Grof S. Caterpillar dreams. London: Hanford Mead, 2004.
53. Grof S. When the impossible happens: Adventures in non-ordinary reality. New York; Sounds True, 2005.
54. Ventegodt S, Thegler S, Andreasen T, Struve F, Enevoldsen L, Bassaine L, et al. Clinical holistic medicine: Psychodynamic short-time therapy complemented with bodywork. A clinical follow-up Study of 109 patients. ScientificWorldJournal 2006; 6:2220-38.
55. Lukban J, Whitmore K, Kellogg-Spadt S, Bologna R, Lesher A, Fletcher E. The effect of manual physical therapy in patients diagnosed with interstitial cystitis, high-tone pelvic floor dysfunction, and sacroiliac dysfunction. Urology 2001;57(6 Suppl 1):121-2.
56. Bergeron S, Brown C, Lord MJ, Oala M, Binik YM, Khalifé S. Physical therapy for vulvar vestibulitis syndrome: a retrospective study. J Sex Marital Ther 2002;28(3),183-92.
57. Ventegodt S, Clausen B, Merrick J. Clinical holistic medicine: Pilot study on the effect of vaginal acupressure (Hippocratic pelvic massage). Scientific WorldJournal 2006;6:2100-16.
58. Wurn BF, Wurn LJ, King CR, Heuer MA, Roscow AS, Hornberger K, Scharf ES. Treating fallopian tube occlusion with a manual pelvic physical therapy. Altern Ther Health Med 2008;14(1):18-23.
59. Leichsenring F, Rabung S, Leibing E. The efficacy of short-term psychodynamic psychotherapy in specific psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 2004;61(12): 1208-16.
60. Leichsenring F. Are psychodynamic and psychoanalytic therapies effective? A review of empirical data. Int J Psychoanal 2005;86(Pt 3):841-68.
61. Leichsenring F, Leibing E. Psychodynamic psychotherapy: a systematic review of techniques, indications and empirical evidence. Psychol Psychother 2007;80(Pt 2):217-28.
62. O´Donohue W, Dopke CA, Swingen DN. Psychotherapy for female sexual dysfunction: A review. Clin Psychol Rev 1997;17(5):537-66.
63. Masters WH, Johnson VE. Human sexual inadequacy. Philadelphia, PA: Lippincott Williams Wilkins, 1966.
64. Struck P, Ventegodt S. Clinical holistic medicine: teaching orgasm for females with chronic anorgasmia using the Betty Dodson method. ScientificWorldJournal 2008;8:883-95.
65. Heiman JR, Meston CM. Empirically validated treatment for sexual dysfunction. Ann Rev Sex Res 1997;8: 148-94.
66. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, et al. Can lifestyle changes reverse coronary heart disease? The lifestyle heart trial. Lancet 1990;336(8708), 129-33.
67. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998; 280(23),2001-7.
68. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 1989; 2(8668):888-91.
69. Levenson FB, Levenson MD, Ventegodt S, Merrick J. Psychodynamic psychotherapy, therapeutic touch and cancer. A review of the method of intervention and study of 75 cases. J Altern Med Res 2009;1(2):165-76.
70. Ventegodt S, Andersen NJ, Merrick J. Rationality and irrationality in Ryke Geerd Hamer's System for holistic

treatment of metastatic cancer. Scientific WorldJournal 2005;5:93-102.
71. Gøtzsches P. Bias in double-blind trials. Dan Med Bull 1990;37:329-36.
72. Ventegodt S, Andersen NJ, Brom B, Merrick J, Greydanus DE: Evidence-based medicine: Four fundamental problems with the randomised clinical trial (RCT) used to document chemical medicine. Int J Adolesc Med Health 2009;21(4):485-96.
73. Boutron I, Estellat C, Guittet L, Dechartres A, Sackett DL, Hróbjartsson A, et al. Methods of blinding in reports of randomized controlled trials assessing pharmacologic treatments: a systematic review. PLoS Med 2006;3(10):e425.
74. Lindholt JS, Ventegodt S, Henneberg EW. Development and validation of QOL5 for clinical databases. A short, global and generic questionnaire based on an integrated theory of the quality of life. Eur J Surgery 2002;168(2): 107-13.
75. Christensen PM, Kristiansen IS. Number-Needed-to-Treat (NNT): Needs treatment with care. Basic Clin Pharmacolol Toxicol. 2006;99(1):12-6.
76. Smith E, Young T. Methods of obtaining good quality research evidence. Community Nurs 1998;4(10): 48-50.
77. Birken CS, Parkin PC. In which journals will pediatricians find the best evidence for clinical practice? Pediatrics 1999 May;103(5 Pt 1):941-7.
78. www.medicine.dk. Accessed Jan 2010.
79. Personal communication. Regulatory coordinator Rikke Bradstrup Haladyn, Danish Medicines Agency, 2009 Dec 14.
80. Gøtzsche PC, Liberati A, Torri V, Rossetti L. Beware of surrogate outcome measures. Int J Technol Assess Health Care 1996;12(2):238-46.

81. Seymour GJ, Gemmell E. Cytokines in periodontal disease: where to from here? Acta Odontol. Scand 2001;59: 167-73.