Ventegodt S, Merrick J. Which types of drugs can be used in evidence-based medicine? A review of metaanalyses and reviews of positive effect, adverse effects, and therapeutic value of whole groups of pharmaceutical drugs. BMJ Dec 7, 2010. http://www.bmj.com/content/341/bmj.c5715.full/reply#bmj_el_246044 Accessed 2010-12-07

Which types of drugs can be used in evidence-based medicine? A review of metaanalyses and reviews of positive effect, adverse effects, and therapeutic value of whole groups of pharmaceutical drugs.

- **Soren Ventegodt**, **Director**
- **Joav Merrick**

Quality of Life Research Center, Copenhagen

To answer the question: "Which types of drugs can be used in evidence -based medicine?" we have made a review of metaanalyses and reviews of positive effects and therapeutic value of whole groups of pharmaceutical drugs.

METHOD

We have searched MedLine (www.PubMed.gov) and journals of alternative medicine often having critical reviews not listed in MedLine, and we have included PhD dissertations and doctoral theses in the search. We found 7 metaanalyses and 4 reviews of whole groups of drugs. The search process was difficult as the concept "drug group" or similar high-level concepts were not commonly used, combined with the enormous number of articles and dissertations (over 20 millions), and compared to this we had limited resources for the study. It is therefore very likely that several relevant meta-analyses and reviews have been excluded. To compensate for that we also used the Danish Drug Directory "Medicin.dk" (1), giving highest priority to meta-analyses, then priority to reviews and finally lowest priority to the drug directory as this is mostly build on single industrial RCTs (2).

RESULTS

Table 1 shows the drug groups that we found general reviews and metaanalyses of. For all drugs, except contraceptives, we found serous methodological problems in the testing (3,4). Most RCTs did not use the proper type of placebo, which is active placebo, needed when the drug has a well-defined toxic

effect. Many RCTs did not include the induction of "spontaneous" dead known to be caused by a wide range of pharmacological drugs (5,6).

The problem of not using active placebo is that a harmful effect of the drug appears as a positive effect in the RCT (6,7,8). In general the outcomes were not clinically relevant but only week surrogate outcome measures (resorption of calcium to bones is a poor indicator of bone strength so number of fractures should have been used; blood pressure is a poor predictor of stroke so stroke rate should have been used etc., see (9)), and the adverse effects were only registered short term, while most adverse effects appears after long term use (see 3). The NNT was not based on healing of patients diseases but almost always on small clinical improvements, giving a wrong impression of low NNT-numbers (3).

Even in the best of the studies many adverse effects were not included in the RCTs, like the well-known loss of sexual desire from many hormonal contraceptives (10).

We found anti-depressant drugs to be almost without effect in one metaanalysis (11) and completely without antidepressant effect in another correction for the use of the wrong type of placebo in the RCTs (in the Cochrane review one study was removed to secure homogeneity and after the exclusion of this study antidepressant drugs were not better than active placebo (8). As there seems to be general agreement about the need for active placebo in such studies (7) the latter analysis is more correct. Antipsychotic drugs did not improve mental state (mental health) but did sedate the patients (reduce "hallucinogenic behaviour"); the outcome "global impression is a mix of these two and behaved accordingly; new drugs were not more efficient or less harmful than Chlorpromazine (12). A large metaanalyses of anti-cancer chemotherapy was found for epitheloid cancers meaning all common cancers, and it showed systematically that anti -cancer chemotherapy did not improve quality of life or survival; as adverse effect were shorter survival and destruction of quality of life (13). As some of the analyses were quite old we repeated them (14,15), but we found the same results again. For NSAIDs we found a Danish doctoral dissertation showing no effect of the group of drugs (16).

Metaanalyses of anti-resoptive (17) and anti-hypertentive (18) drugs shows little effect on clinically relevant outcomes; many studies only used indirect measures with low correlation to the actual clinical problem. While there seem to be some effect of these drugs the NNT numbers are still so high and the NNH and NNHtotal numbers so low that the therapeutic value is much less than one, which means that the drugs are likely to course more harm than benefit for the patients.

For anti asthma corticosteroids, antibiotics, anti-inflammatory drugs, antihistamines, anti-cholinergic drugs, anti-AIDS retroviral drugs, hypnotics, sedatives and contraceptives we found fair therapeutic effect but still massive methodological problems (except for contraceptives where only one major adverse effect in general was missing) (see table 1 for references).

Table 1: Effect, adverse effects, and Therapeutic Value (TV) of major pharmacological drug groups, listed according to Therapeutic Value (calculated as TV=NNHtotal/NNT). (NNT: Number Needed to

Treat; NNH: Number Needed to treat to Harm; NNHtotal: The total likelihood to get one or more adverse effect or event, expressed as NNH)

Drug group	NNT	NNH_{total}	TV	Serious methodological problems in RCTs?	References
Anti-depressant	∞	1-3	0	Yes	8,11
Anti-psychotic	∞	1	0	Yes	12,14
Anti-cancer chemotherapy	∞	1	0	Yes	13,16
NSAIDs	∞	10	0	Yes	16
Anti-resorptive (calcium in bones)	50	10	0.1	Yes	17
Anti-hypertensive	20	3	0.1	Yes	18
Anti-asthma corticosteroids	3	2	0,67	Yes	19
Morphine type	3	3	1	Yes	5
Antibiotics	5	5	1	Yes	5
Anti-inflammatory	5	5	1	Yes	5
Antihistamines	3	3	1	Yes	5
Anti-AIDS (anti-retroviral)	3	3	1	Yes	20
Sedatives	1	1	1	Yes	5
Hypnotics	1	1	1	Yes	5,21
Contraceptives	1	10	10	No*	5

*sexual desire is severely compromised (NNH=3) for many oral contraceptives and this is often as an adverse effect.

DISCUSSION

Many classes of drugs are not included in this analysis due to lack of data. We noticed the pattern that when large meta-analysis was made including all studies of all drugs in a drug-group, and including also unpublished data of negative findings, the drug-type often was found to be ineffective and harmful. Most of the drug types in table 1 that came out as efficient and fairly safe drugs have not been that thoroughly tested, leaving the possibility that higher quality meta-analyses will document less efficacy and more harm. Also, almost all the studies suffer from rather severe methodological problems, because of the many problems associated with the RTC-test (3,8,11).

ACKNOWLEDGMENTS

The Danish Quality of Life Survey, Quality of Life Research Center and the Research Clinic for Holistic Medicine, Copenhagen, was from 1987 till today supported by grants from the 1991 Pharmacy Foundation, the Goodwill-fonden, the JL-Foundation, E Danielsen and Wife's Foundation, Emmerick Meyer's Trust, the Frimodt-Heineken Foundation, the Hede Nielsen Family Foundation, Petrus Andersens Fond, Wholesaler CP Frederiksens Study Trust, Else and Mogens Wedell-Wedellsborg's Foundation and IMK Almene Fond. The research in quality of life and scientific complementary and holistic medicine was approved by the Copenhagen Scientific Ethical Committee under the numbers (KF)V. 100.1762-90, (KF)V. 100.2123/91, (KF)V. 01-502/93, (KF)V. 01-026/97, (KF)V. 01-162/97, (KF)V. 01-198/97, and further correspondence. We declare no conflicts of interest.

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Soren Ventegodt, MD, MMedSci, EU-MSc-CAM (1,2,3,4,5) and Joav Merrick, MD, MMedSci, DMSc (5,6,7,8)

1 Quality of Life Research Center, Copenhagen, Denmark; 2 Research Clinic for Holistic Medicine and 3 Nordic School of Holistic Medicine, Copenhagen, Denmark; 4 Scandinavian Foundation for Holistic Medicine, Sandvika, Norway; 5 Interuniversity College, Graz, Austria; 6 National Institute of Child Health and Human Development, 7 Office of the Medical Director, Division for Mental Retardation, Ministry of Social Affairs, Jerusalem, Israel and 8 Kentucky Children's Hospital, University of Kentucky, Lexington, United States

Competing interests: None declared

Published 7 December 2010