«Ten Commandments» for Psychopharmacology

Patients with mental disorders are often treated with combinations of drugs that have no documented effect, in doses which are not recommended and for non-approved indications. They are treated according to «treatment practice» and «clinical discretion», and there is insufficient follow-up of the drug treatment. In our opinion, this leads to some patients being overtreated and others undertreated, with therapeutic failure and adverse effects as a consequence.

You visit the emergency department because of a sore throat. After being examined, you are given a prescription for an antibiotic. A week later, you are just as ill. Your GP believes that a different drug will be more effective and prescribes this in addition, since it cannot be precluded that your condition might have been even worse without the first drug. After two weeks of treatment, you are fortunately almost recovered. However, your doctor wants you to continue taking half the dosage of both drugs for a while longer to prevent a relapse. He also prescribes an anti-viral drug, since it is not completely certain that bacteria were the cause of your illness.

This is not a true story. Doctors in Norway must not treat infections in this manner. However, if we change the story slightly and substitute throat infection and antibiotics for mental disorder and psychopharmaceuticals, the scenario is unfortunately not as improbable.

Therapeutic recommendations for mental disorders are easily available, and guidelines and indications have been prepared for each drug (1). There are several recommendations for appropriate drug treatment (2, 3). Nevertheless, experience with psychiatric and pharmacological departments has shown us that patients are commonly treated with drug combinations that are not documented, in doses that are not recommended and for non-approved indications. We see this daily on requisition forms, in blood tests and among patients at our psychopharmacological outpatient clinic.

Mental disorders are often chronic, with a fluctuating course, and there are few biological tests which are relevant. There is a widespread practice of trusting «clinical discretion» and «therapeutic tradition». Patients with mental disorders are frequently treated with medicines for symptoms such as pain, anxiety, insomnia and indigestion in addition to drugs to treat somatic diseases. They may therefore end up with a high consumption of drugs.

When we are faced with a problem that apparently cannot be solved using the established guidelines, it is easy to try something new – such as increasing the dose, combining the initial drug with new drugs and giving drugs to combat the adverse effects that arise. But patients with mental disorders deserve better than treatment by trial and error. Psychopharmacological therapy should follow the basic rules for quality work: plan, act, check and correct. Here follows our recommendation.

The «Ten Commandments»

1. *Make the correct diagnosis and know for which indication you are prescribing the drug*
   Correct diagnosis is a prerequisite for correct treatment. Not all patients with symptoms of depression should have antidepressants, and not all uneasiness is anxiety. If treatment precedes diagnosis, it may affect the course of the illness in such a way that it becomes difficult to make the correct diagnosis and provide optimal therapy.

2. *Have a goal for the therapy*
   Psychotherapy works, and contact with a therapist will improve symptoms in most patients. You should therefore have a goal for the drug therapy, and this goal must differ from the natural course of the disorder with no intervention. If drugs are not considered to have any efficacy beyond the natural course of the illness or psychotherapy, see commandment 6.

3. *Be certain that you are prescribing the drug in the right dosage and for a sufficient duration*
   The same dosage may have different effects; there is a great degree of individual variation in the metabolism of drugs. Dosages which are effective in one patient may give rise to adverse effects or therapeutic failure in another. Differences in treatment efficacy and the prevalence of adverse effects can often be explained by differences in serum concentration and concentration at the site of action (4). Psychopharmaceuticals have complex mechanisms of action and their effect is the combined result of rapid binding at receptor level and slower intracellular processes. It therefore takes time to ascertain the efficacy of a drug.

4. *Treat one disease with one drug*
   Combination therapy is one of the most widespread, but also one of the most poorly documented principles in psychopharmacology. There is little scientifically documented beneficial effect of combination therapy (5). Combination therapy increases the risk of adverse effects and reduces compliance (6). Since the mechanisms of action for each drug are only partly known, it is difficult to predict the effect of combining different drugs. Combination therapy renders it difficult to find the right dosage, to assess the effect of changes in dosage, and to ascertain the cause of adverse effects. If there is a need for combination therapy, see commandments 1 and 3.

5. *Never treat adverse effects of drugs with drugs*
   Adverse effects are common. All psychopharmaceuticals have adverse effects of varying degrees of severity. Adverse effects must be thoroughly investigated, and should be dealt with by checking the dosage, assessing possible interactions or changing drugs. Adding new drugs entails a risk of new adverse effects, interactions and tolerance. The use of drugs to treat unwanted adverse effects must be the final recourse after all other measures have been considered.

6. *Discontinue drugs that have no effect*
   Many patients end up using more drugs than they need. This may be because the treatment was commenced in an emergency situation with high symptom intensity, drugs were added on a false premise, or tolerance developed. It may appear easier to add new drugs when the treatment fails than to discontinue those which are ineffective. We should be critical of all drugs and, in case of doubt, discontinuation under clinical supervision should be considered.

7. *Make only one change at a time*
   Treating a mental disorder can often lead to a perceived sense of urgency. The patient is suffering, the department director wants the patient discharged quickly, and the next of kin are worried that not enough is happening. This results in pressure to do something – frequently several things simultaneously. It may be difficult to assess clinical effect and adverse effects when the treatment changes. If several changes are made at the same time, it becomes impossible to know the effect of each change. Two interventions may also counteract each other in accelerator/brake-type interactions.

8. *Remember that the illness you are treating is not always the patient's only illness*
   There is often significant comorbidity in mental disorders which may affect and complicate the treatment. Interactions between drugs may result in therapeutic failure or adverse effects. Thorough assessment and good communication with the patient and other treatment providers is the key to proper treatment.

9. *Be aware that patients take drugs and medications which they do not tell you about*
   A number of drugs, including those for somatic disorders, have effects and adverse effects that may resemble symptoms of mental disorders. Patients do not always volunteer information about their use of other drugs (7). Natural remedies and nutritional supplements may also cause serious side effects and interactions, as may substances of abuse. It is therefore important to obtain information about all such use.

10. *Do not treat patients by trial and error*
    Trial and error is a common approach in psycopharmacology. This increases the risk of therapeutic failure. With every unsuccessful treatment attempt, compliance and the placebo effect are reduced. Make a thorough assessment of the efficacy and adverse effects of previous drugs used. Also investigate whether serum concentration measurements and pharmacogenetic analyses have previously been undertaken. Proper planning of the treatment increases the probability of success.

We also wish to offer a final piece of advice:

Be critical and remember that therapeutic traditions are not always based on scientifically documented facts

Be critical of established practice. Is it scientifically based? Be prepared to try new forms of treatment when new knowledge indicates this. Take into account that research results are usually based on large groups of patients. If you remember that the patient you are treating is unique in terms of their background, genetics, clinical picture and other illnesses, you will have a good basis on which to be able to provide assistance.

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References

1. Statens legemiddelverk. www.legemiddelverket.no (26.11.2014).
2. Glick ID, Balon RJ, Ballon J et al. Teaching pearls from the lost art of psychopharmacology. J Psychiatr Pract 2009; 15: 423–6.
3. Salzman C, Glick I, Keshavan MS. The 7 sins of psychopharmacology. J Clin Psychopharmacol 2010; 30: 653–5.
4. Murray M. Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. J Pharm Pharmacol 2006; 58: 871–85.
5. Glick ID, Pham D, Davis JM. Concomitant medications may not improve outcome of antipsychotic monotherapy for stabilized patients with nonacute schizophrenia. J Clin Psychiatry 2006; 67: 1261–5.
6. Hoffman DA, Schiller M, Greenblatt JM et al. Polypharmacy or medication washout: an old tool revisited. Neuropsychiatr Dis Treat 2011; 7: 639–48.
7. Tveito M, Bramness JG, Engedal K et al. Psychotropic medication in geriatric psychiatric patients: use and unreported use in relation to serum concentrations. Eur J Clin Pharmacol 2014; 70: 1139–45.

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