On the necessity and possibilitiy on minimal use of neuroleptics

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This text is a summary of arguments, that supports the idea of selective and low dose application of neuroleptcs for so called schizophrenics and other psychotic disorders.

Schizophrenia and the Dopamine-System

The neurobiological changes in the dopamine system in patients diagnosed with schizophrenia are rather subtle. Recent PET-Scan studies show a normal number of D2 receptors in patients diagnosed with schizophrenia[1]. The gene expression of the 5 different dopamine receptors in schizophrenics does not differ from that of controls.[2] Only during the acute psychosis there is an increased phasic presynaptic dopamine release[3]. This comes to an end during remission from acute psychosis. This has been described as the "phasic sensitisation" of the subcortical striatal dopamine system.[4] The exact mechanism, that results in a termination of this sensitisation and a true remission of the psychotic episode is as yet unknown.

In the prefrontal region of the brain in a majority of people diagnosed with schizophrenia there is tonic deficit of dopamine transmission at the predominant D1-receptors in this region. This is considered to be one neurobiological substrate for negative symtoms, decreased neurocognition and for the extreme susceptability to stress of the dopaminergic system[5]. These findings are meaningful in helping to understand the effects of neuroleptics.

Long term course of Schizophrenia

Approximately 70% of „schizophrenic" psychoses are of an episodic nature, with a different degree of negativ symptoms during the interval. Approximately **45-60%** of these patients have a good outcome in follow up studies, even multiple episodes in these patients do not result in an increase of possibly existing residual symptoms.

The definition of schizophrenia in newer diagnostic systems such as the DSM IV is more narrow than in older diagnostic manuals such as the DSM III. Consequently, older follow up studies have slightly better results than those current studies.

In an intercultural comparison study of the WHO (DOSMed)[6] people diagnosed with schizophrenia in developing countries (India, Nigeria, Columbia) which were rarely treated with neuroleptic medication (2,6% - 16,5% in the differnet regions of the study) showed significantly less episodes and greater number of complete remissions. In the 3 rural regions a significant precentage of patients had only one episode (42% - 54%) in comparison to industrial nations (6%-32%).

The better outcomes in social and family structures in the Third World and the significantly better long term outcomes in specifically active and recovery oriented treatment systems such as the Vermont Rehabilitation Study[7] show that the extensive chronicity and social dependence are not an inherent outcome of the disorder itself. Substantial psychosocial and treatment contingent influences have to be assumed.[8]

Neuroleptics and D2 receptor antagonism

All neuroleptics do not effect the increased presynaptic dopamine release during the acute episodes but antagonize the postsynaptic D2 receptors. This has different consequences.

They block the postsynaptic D2 receptors and continue to do so when the phasic

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increased dopamine release is normalised. There is a therapeutic window for the antipsychotic effects between 50-80% D2 receptor blockade.[9] The effective threshold level for the different neuroleptics can be different within this range. For clozapine the level is only between 40-60.[10]
Dosages of 2 mg Haloperidol equivalents will block more than 60 - 70% of the dopamine receptors.[11] Blocking more that 60-80% of DA receptors will result in an occurance of extrapyramidal side effects (EPS), hyperprolactinemia, neuroleptic induced negative symptoms (NIPS), neuropsychologischen deficits (and other side effects)[12].
Above this threshold of receptor occupancy the modulating serotonergic mechanism of atypicals (5HT2A-receptor antagonism and 5HT1A-receptoren agonismus does not exist.[13]

D2-Receptor Upregulation

D2-occupancy by neuroleptics causes compensatory upregulation[14] effects starting within just a few weeks or month depending on dosages. This upregulation leads to additional 34 % (mean) up to 98% subcortical D2 receptors in striatum und thalamus.[15]
A subgroup of patients with poor treatment response shows an early upregulation within 25 days[16].
Supposedly the following effects can be attributed to this upregulation:

- an increase in dosage during the course of treatment: partial neuroleptic tolerance
- short term rebound phenomena when medication is disconitiued[17]
- 3 to 6 fold increased relapse rate after abrupt neuroleptics withdrawal[18]
- increased positive and negative symtoms in subsequent episodes[19]
- serious tardive dyskinesia in patients with the highest upregulation[20]
- dose-dependent neuroleptic induced hypertrophy of subcortical structures (basal ganglia , thalamus) which correlates with the amount of positive and negative symptoms[21]
- neuroleptica induced dopamine sensitivity resulting in increased vulnerability for psychosis[22]
- neuroleptica induced supersensitivity resulting in so called "breakthrough" psychoses during neuroleptic treatment [23]

Consequently, there are significantly fewer relapses in studies with selective neuroleptica free acute treatment in this subgroup.[24]
Patients with low dosages have a higher chance of discontinuing neuroleptics.[25]
Therefore we can assume, that high **relapse rates (with a revolving door effect)** in premature and prescribed discontinuation of neuroleptics is partially an effect of the use of neuroleptics itself.

Partial and Non-Responder

Positive symptoms also develop as a result of non dopaminergic mechanisms. Only 30% of the variance of productive symptoms can be explained by dopaminergic mechanism.[26] This may also be the reason why 20% of acute psychotic patients are resistant and more partially resistant to the normal D2 blocking neuroleptic treatment. Thus in cases of partial remission full remission generally cannot be forced by augmenting the dosage as this is more a question of time than dosage. Higher dosages results in worse remission than lower dosages.[27] Unfounded preemptive dosage increase – a frequent practice in day to day practice - produces additional negative and seriously damaging effects, that will be presented later. Instead it is more sensible to assume an observant position along with the use of specific therapeutic treatment like providing safety and non intrusive "being with".[28]

Neuroleptica and D1 Receptor

D1 receptors are the most important dopamine receptors of the neocortex, especially in the prefrontal region, that is functionally hypodopaminergic in the majority of patients diagnosed with schizophrenia. Neuroleptics (except for Amisulprid) antagonize the D1 receptors and will result in the down regulation of the D1 receptors in a dose-dependent manner. (For more details please see chapter neurocognition.)
This has negative effects on the amount of negative symptoms, further impairs neurocognition and elevates the stress vulnerability of the dopaminergic system for psychotic symptoms.[29]

Negative-Symptomatology

Primary negative symptoms are seen as disease inherent and relatively continuous. Secondary negative symptoms are mostly due to individual and social reactions to the disease and more time limited.
Negative symptoms are also the result of constant postsynaptic D2 and D1 blockage through neuroleptics. It was not before 1993 that a neuroleptic-induced deficit syndrome (NIDS) was described with akinesia, parkinsonism, akinetic depression, sedation, lack of energy, emotional withdrawl, reduced creativity, difficulties in directing thoughts by will and thought deprivation as a consequence of taking neuroleptics.[30]
All three forms of negative symptomatolgy have one thing in common that they cannot be definitely differentiated from one another.
In experimental studies the extent of neuroleptic D2 blockage correlates with negative symptomatology, hence the smaller the D2 blockage the fewer the negative symptoms.[31]
To this day there is no atypical that has been approved by the FDA for the treatment of negative symptoms.
In comparison studies of atypical and typical neuroleptics **positive, but marginally small effects are found under monotherapy and low doses of 50-100mg Amisulprid (r=0.14)**[32], (however this effect is no longer present at 150 mg[33]) and **monotherapy with 5mg Olanzapin (r=0.08)[34],** in case of predominant positive symptoms also with higher dosages [35]. For risperidone the results are inconsistent.[36]
For aripiprazole there are until today only 2 independent studies with also marginally small positive effects.[37]
With no other atypical any not even small effect compared to haloperidol could be demonstrated. Quetiapin was even slightly worse (r=-0.05)[38].
In patients with **persistent negative symptoms** no significant effects of neuroleptics were found.[39]
This marginal effect of neuroleptics on negative symptoms is supposedly to be seen as remission effect of positive symptoms. Neuroleptic-induced negative symptoms lower this effect. The additional effect of low dose amisulpride and olanzapine on negative symptoms is probably just result of a lesser NIDS under these dosages.
For olanzapine an additional serotonergic attenuation of dopaminergic transmission through antagonism of 5HT2A-receptors and agonism of 5HT1A-receptors is discussed.[40]
Already above 2 mg haloperidol equivalents this effect is suspended.[41]
With amisulpride some effect on presynaptic dopaminergic autoreceptors might play a role.[42]
Comparison studies with **placebo control groups** show higher effect sizes (r= 0.19-0.26) of atypicals than placebo.[43] Placebo control groups consist of patients with previous neuroleptic treatment and NIDS on the one hand and upregulation effects with higher rebound and relapse rates after withdrawl on the other. Patients are included in these

control groups after 1 to 4 weeks after quite rapid withdrawl (only one study 6 weeks after withdrawl). The washout phase for negative symptoms of 4 weeks is too short to rule out long lasting NIDS.[44] In case of exacerbations negative symptoms can also increase. Therefore the small statistical effect is - at least partially - an artefact of the previous neuroleptic medication but not a clinically significant reduction of true negative symptoms.

Accordingly, it is important to use relatively small dosages already during acute treatment and even lower thereafter to avoid negative symptoms.

Negative symptoms, that occur under a neuroleptic dosage higher than 5 mg Olanzapin or 100 mg Amisulprid or under another neuroleptic are presumably partially or fully a result of a neuroleptic-induced deficit syndrome.

However, most patients in the acute phase and afterwards continually recieve a dosage beyond the recommended maximum and are consequently suffering from neuroleptic-induced deficit syndrome. For several patients the dosages they are recieving are above the prescribed limits that are suggested, often also as a result of combination treatment. The long term negative effects for rehabilitation and recovery through the additional pharmacological blockage of the dopaminergic system are substantial. They included restricted affect, motivation, energy, drive and neurocognitive function.

In addition: as negative symptoms can also have psychological reasons, defensive and protective functions, psychosocial interventions are also effective but are often not offered to patients.[45]

Neurocognition

Neurocognition includes working memory, verbal memory, attention, processing speed, exceutive functions, problem solving, logical thinking and is a funtion of the prefrontal cortex.

In the prefrontal cortex (e.g. dorosolateral prefrontal cortex) of most patients diagnosed with schizophrenia there is (probably) a constant hypodopaminergic state[46] with compensatory (no medication effect) but inefficent upregulation of the presenting D1 receptors[47].

Neuroleptics cause:

(1) **a blockage of D1 receptors (= D1 antagonism) (except** for Amisulprid).

(2) a dose dependent down regulation of **D1** receptors especially in the frontal and temporal cortex [48] presumably as a result of the D2 blockade [49] and therefore pertaining to all neuroleptics.

(3) possible further yet unknown mechanism because Amisulprid has no clinically proven advantage.[50]

(4) medium and long term neuroleptics induced a frontal neurodegenaration.

These effects of neuroleptics additionally impair the already constrained neurocognition in people diagnosed with schizophrenia.

(5) further atypical neuroleptics have a principally favorable dopamine releasing effect. He is either due to a direct **5HT1A-agonism or an indirect and synergistic D2 – and 5HT2A-antagonism**[51], at best - however only for low dosages[52] and maybe only time limited. Its long term persistence is not proven.[53] This can compensate for the other (1-4) negative neurocognitive side effects of neuroleptics but clinically this does not result in an overall positive net effect of atypicals on neurocognition.

A comparison study between „low dose" **haloperidol** (average of 5 mg) and **risperidone** (average of 6 mg) showed no verifiable difference in neuropsychological tests after 6 months[54]. In another similar comparison study[55] on **haloperidol** (4.6 mg) vs. **olazapine** (9.6 mg) after 12 weeks of acute treatment of schizophrenic and schizo-

affective patients with first episode the effects of 0.20 vs. 0.36 were small and not significant[α].

In a substudy of the CATIE trial tests carried out after 2, 6 and 18 months showed an improvement in neurocognition of all subjects in the first 8 weeks[56]. The differences between the different neuroleptics however wer not significant.[β] There were only minimal further improvements (+11%) between the 2nd and 18th month (303 of intially 817 patients). At 18 month the perphenazine group showed significantly better results.[γ]

Presumably the initial improvement of neurocognition is predominatly a remission effect of the acute psychosis and not a direct effect of the medication. As neurocognition is impaired by acute symptoms like disorganisation[57], formal thought disorder[58], delusions[59] and hallucinations[60] this effect will decrease after their remission.

We must therefore assume that neuroleptics- typicals and atypicals- based on their mechanism of action result in an additional disturbance of neurocognition.

The neurocognitive improving effect of D1 agonists (experimental studies) supports this idea.[61]

Only to **Clozapin** a net improvement could be attributed based on its partial D1-agonism. Only studies with neuroleptic free control groups can provide the necessary proof of an absolute improvement of neurocognitive functioning by means of neuroleptics.

Neurodegeneration

According to new imaging studies short term 2-8 week use of neuroleptics[62] is enough to cause reduction of gray matter especially in the frontal regions of the brain. There are 6 highly regarded published studies on this topic.[63]

This reduction is most likely dependent on cumulative dosages. It also correlates with neuopsychological deficits[64]. It possible that there is a patient group with a marked reduction[δ].

With high probability the atrophy of grey matter is also a result of atypicals however lower.

There are also studies, in which no signifiant differences between typicals and atypicals can be seen.[65]

In two longitudinal studies carried out during a psychotic exacerbation without neuroleptic medication they found an increase (!) of grey matter in the frontal and temporal regions of the brain and overall[66] and a decrease in ventricle size[67] and a reverse effect when followed by neuroleptic treatment.

Animal studies showed a reduced density (-39%) of postsynaptic dendrite nerve endings in rats after long term haloperidol intake of 6 months[68], that was both reversibel[69] or not reversibel[70] after a longer neuropleptic free period. Animal studies on rats show that under the influence of haloperidol as with risperidone (however the effect

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α „The differential effect of the two treatments accounted for 2.2% of the variance in neurocognitive change".

β „At 2 months, treatment resulted in small neurocognitive improvements of z = 0.13 for olanzapine (P<.002), 0.25 for perphenazine (P<.001), 0.18 for quetiapine (P<.001), 0.26 for risperidone (P<.001), and 0.12 for ziprasidone (P<.06), with no significant differences between groups. Results at 6 months were similar."

γ "Pairwise comparisons suggested that improvement in the neurocognitive composite score was greater in the perphenazine group (0.49) than in the olanzapine group (0.15; *P*=.002) or the risperidone group (0.28; *P*=.04). The ziprasidone and quetiapine groups did not differ from any of the other treatments."

δ Aus den publizierte Daten der Lieberman et al (2005) Studie lässt sich aufgrund der breiter Streuung um den Mittelwert unter Haloperidol eine Neurodegeneration von **mehr als 4%** der gesamten Grauen Substanz **nach 2 ¼ Jahren** mit 2 behandelten psychotischen Episoden für 16% der untersuchten Patienten errechnen. Die Dropout rate ist jedoch erheblich.

is smaller here) there is an apoptosis (cell loss) of cortical neurones induced through D2 receptor blockage.[71] This is dose and duration dependent. We must therefore assume that atypicals do not generally have another mechanism. There 5HT2A antagonism might have a certain protective function, however this is only likely for low dosages.[72] In experiments with apes the neurodegenerative effect under atypicals is as pronounced as under typical neuroleptics.[73]

Further, we must consider underlying **artefacts** in imaging procedures through increased brain weight as a result of increased body weight through neuroleptic treatment (especially under olanzapin and clozapine), that (partially) mask the extent of substance specific neurodegeneration.[74]

In contrast to these findings a study of patients taking risperidone (n=17) and clozapine (n=12) showed an increase in grey matter under neuroleptics after 2 years in the parietal and occipital (most), and in the frontal cortex for patients taking clozapine.[75] The increase in gray matter was not statistically associated with an increase in weight. The authors themselves concluded: ”Thus, it seems unlikely that the increase in GM observed in our patients was caused by the appearance of new neurons or increased connections.” So far there is no experimental evidence for stable neurogenesis through atypicals. Neurones of a clozapine induced cell division did not survive beyond 3 weeks.[76] The authors believe that a proliferation of glial cells is more likely. This has been found true in rats taking olanzapine[77], however in small numbers without clinical relevance. It should also be noted that there is a significant decrease in white matter with time. According to the authors this reduction of white matter due to symptom remission also speaks against a neurogenesis of intact cells, because the development of such cells should also show an increase in white matter.

In patients that are optimally treated with neuroleptics there is still a significant decline between the 5th and the 9th year for parameters such as verbal memory and problem solving ability as well as language and motor skills.[78] This progressive detrioration after the 5 year of illness contradicts the general expectation and is possibly a result of neurodegeneration by neuroleptics. Animal experiments on potential reversibility as mentioned earlier are currently showing contradictory results.

In spite of these findings recent imaging studies do not take into consideration the effect of neuroleptics as a confounding factor. A new study from 2007[79] still interprets the reduction of frontal and temporal grey matter under typical neuroleptics as resulting from the disorder itself. The continued increase in neurodegeneration during rehospitalisation is only explained as a result of the excacerbation and not related back to the medication effect. The diminished reduction of grey matter under clozapine and olanzapine (but not with other neuroleptics) is interpreted as attenuation of the neurogenerative process of the disorder, however the weight gain by change of neuroleptic treatment to one of the two substances (71 of 95 patients) is not controlled for.

Beyond this there is also a neurodegeneration which is independent from any neuroleptic treatment and probably starts at the beginning of the disease.[80] Causes are unexplained. Anormalities of synaptic plasticity, anormal maturation of the brain, stress effects or other environmental factors are discussed.

Effects of neuroleptic medication or other independent ones cannot be clearly distinguished from each other, especially because there are no long term control groups of patients treated without neuroleptics. Therefore currently the neuroleptic-induced neurodegeneration can only be calculated from correlations with the cumulative dosages of ingested neuroleptics.

Mortality

Life expectancy for people with serious mental illness in the USA is currently reduced by 25-35 years[81]. Neuroleptics holds their share in this excess mortality. The standardized mortality rate (SMR) of people diagnosed with schizophrenia has been on the rise during the last 30 years. The gap in mortality to the general population and those with schizophrenia has increased.[82] In an epidemiological study in Massachusetts (USA) from 1998-2000 subject with serious mental illness in the age between 45-54 Jahren had the highest mortality risk for heart diseases – ten years before the general population – and in the age between 25 -44 the kardiovaskular mortality was 6,6-fold higher than in the general population.[83] Particuliarly in the middle aged group the age specific mortality risk is especially high. One can assume that the early emergence of cardiovaskular risk faktors and diabetes under neuroleptics makes a significant contribution to it.

In the International Study of Schizophrenia of the WHO (ISoS[84]) the 5 highest standard mortality ratios (SMR > 4.0) can be found in the research areas of most developed countries (Dublin, Mannheim, Nagasaki, Hong Kong, Groningen).

Since 2000 there has been more than 14 **studies** [85] investigating the **increased mortality through neuroleptics** published in high ranking journals. This is mostly a result of cardiac arrythmia and metabolic side effects (lipids, diabities, obesity).

The rate of **sudden death** in the normal population is 0,7/1000 individuals per year[86]. Mostly through prolonged QTc-intervals above 500msec plus further risk factors torsades de pointes (polymorphic ventricular arrhythmia) can develop, which degenerate into ventricular fibrillation and lead to sudden death. Monotherapy (dose dependent) and polypharmacie of neuroleptics or a combination with other substances like antidepressants (tricyclic, tetracyclic, SSRI, Venlafaxin), Lithium and other like antibiotics, antiarrhythmics, antihistaminics can cause this.

Severe cardiovascular disease, e.g. caused by a neuroleptic-induced metabolic syndrome, also increases the risk of sudden death under neuroleptics.[87]

40-50% (and more) of patients treated with neuroleptics over a long period of time suffer from **metabolic syndrome.**[88] The rate in naturalistic studies is clearly higher than in industry dependent ones.[89] Defined symptoms are: abdominal obesity, high triglycerides, low HDL cholesterol and high LDL cholesterol, elevated blood pressure, Insulin resistance or glucose intolerance, diabetes.

The contribution of neuroleptics to this elevated rate is difficult to quantify but surely high. The prevalence of the metabolic syndrome in the adult general population in Germany is about 20%[90] in the United States about 24%.[91] Before the onset of schizophrenic symptoms affected men have a lower BMI (Body-Mass-Index) than the non-affected.[92]

Neuroleptics can also cause impaired glucose tolerance, new onset type 2 **diabetes**, worsening of existing type 1 and 2 diabetes and potentially fatal ketoacidosis.[93] Comparison studies with untreated patients with schizophrenia do account for a causal relation.[94] In addition there is some evidence, that people with psychotic disorders have an impaired glucose tolerance (higher fasting glucose level and elevated oral glucose tolerance test), which might be of genetic origin.[95] But his was not confirmed in a second study.[96] And could also be – according to the authors - a result of elevated stress during the acute psychosis.

But particularly a possible additional genetic predisposition obliges to special therapeutic cautiousness.

Sudden death and metabolic syndrome and diabetes are dependent on:

(1) the neuroleptic **substance**. **Sudden death** can be caused by Thioridazin, Phenothiazine, Thioxanthene, Butyrophenone, Sertindol, Ziprasidon, Clozapin.[97] **Metabolic syndrome** und **diabetes** by olanzapine and clozapine, quetiapine, risperidone and other typicals, primarily phenothiazine. Also amisulpride can cause a metabolic syndrome, ziprasidone possibly diabetes[98]
Recent animal studies[99] confirm that drugs with anticholinergic properties may affect insulin secretion through a direct effect on pancreatic islets cells via muscarinic $(M)_3$ receptors. Several atypical antipsychotics bind to M_3 receptors in the pancreas and act as receptor antagonists, thereby **inhibiting insulin secretion**. Therefore insulin-resistence due to adipositas cannot be compensated by more insulin secretion or in about ¼ of the cases a direct effect of neuroleptics on insulin secretion without previous adipositas can cause diabetes[100].
High M3 receptor binding affinity: clozapine, olanzapine, chlorpromazine, thioridazine.
Also the antidepressants amitriptyline, doxepine, imipramine, paroxetine.
Medium M3 receptor binding affinity: aripiprazole, quetiapine; pimozide, perphenazine, fluphenazine, trifluoperazine.
Low M3 receptor binding affinity: ziprasodone, risperidone, haloperidol, thiothixene.[101]

(2) the **dosages**: especially in cases of sudden heart failure[102], cardiovascular death, metabolic syndrome[103] and diabetes[104]. For combination treatment the total dosage of all neuroleptics taken must be considered.
To my knowledge there are no studies in which the dosage of neuroleptics – if at al collected - was not directly correlated with sudden death, metabolic syndrome and diabetes, even within in the low dose range.[105]

(3) the number of simultaneously prescribed neuroleptcs (= **polypharmacy**). Polypharmacy increases the risk of sudden cardic death[106], as well as diabetes[107] and metabolic syndrome[108]. There are two studies which do not find this connection.[ε]

In spite of all this high dosages-even above and beyond recommended dosages- as well as combination treatment are on the rise. A study in the UK from 2002 on 3132 patients showed that 20% had dosages above recommend range and 48% had more than one neuroleptic.[109] This is a sign of therapeutic helplessness resulting from reductionistic biological models of illness and insufficient treatment milieus and structures.
According to a scandinavian study within the general population the risk for coronary heart disease and stroke is 3-fold elevated and the cardiovaskular **mortality** is 5-fold elevated within 6.9 years.

ε Montout, C., Casadebaig, F., Lagnaoui, R., et al (2002). Neuroleptics and mortality in schizophrenia: prospective analysis of deaths in a French cohort of schizophrenic patients. Schizophrenia Research, 57, 147-156.
Kommentar: Prospektive Studie über 4 Jahre an 3325 Pat mit Durchschnittsalter 39 J bei Beginn, 87 % Typika, 51% Polypharmazie, ca. 4% ohne Neuroleptika in dem Zeitraum, 13 % Adipositas, 3% Diabetes, Todesrate insgesamt 4,4%, Haupttodesursache Suizid, nur unter Atypika erhöhte Mortalitätsrate (= „anderer Todesursachen"). Keine Korrelation mit Polypharmazie. Grobe Klassifikation der Todesursachen, Keine Erfassung der Dosishöhe.

Morgan MG, Scully PJ, Youssef HA, Kinsella A, Owens JM, Waddington JL.(2003) Prospective analysis of premature mortality in schizophrenia in relation to health service engagement: a 7.5-year study within an epidemiologically complete, homogeneous population in rural Ireland. Psychiatry Res. 117(2):127-35.
Kommentar: Prospektive Studie an 72 überwiegend jüngeren ambulanten Patienten über 7,5 Jahre mit Polypharmazie (Typika) mit überwiegend 2 NL in 27% d. Fälle. Keine Rekonstruktion der genauen individuellen Todesursachen.

Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L.(2001): Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 24(4):683-9.

According to Correll a **metabolic syndrome by atypicals doubles the 10 year risk** (risk ratio 2.16) of coronary heart disease: angina pectoris, heart attack and sudden death. Further, secondary diseases are cerebro-vascular and other vascular diseases, diabeties (with the potential complications of ketoacidosis und nekrotic pancreatitis) dementia and a further increase of the deathly torsades de pointes. Malignes neuroleptic syndrome[110], pulmonary embolisation[111], asthma[112], cardio myopathie und myocarditis[113], ileus[114] und asphyxia[115] are to be added. Men probably have a greater risk (risk ratio 3.56) for cornary heart disease if they suffer from metabolic syndrome than woman. Patients with a **metabolic syndrome and diabetes have a 7-fold higher risk** (risk ratio 7.17) for coronary heart disease within 10 years.[116]
But also a nondiabetic level of glucose intolerance above 99 mg/dl[117] is a risk factor for heart attacks[118] and other kardiovaskulär events[119].
As Jin et al put it: Diabetes may represent only the ”the tip of the proverbial iceberg... impaired glucose tolerance in the nondiabetic range…represents a source of ongoing cardiovascular risk even if the patient does not develop overt diabetes mellitus.”[120]
A finnish general population survey from 2000 detected that 22% of the patients with a schizophrenia diagnose (and treatment with typicals in 88% of the cases) developed a type 2 diabetes compared to 6,1% of the inhabitants without psychosis.[121]
This risk for coronary heart diseases is further increased by **smoking,** an additional risk ratio of **1.76** in a study of 367 patients[122]. It is important to consider that the number of cigarettes and the extent of neuroleptic D2 blockade are significantly correlated[123]. Thus the toxicity and mortality caused by smoking are also a result of neuroleptics.
Atypicals have a lower risk für tardive Dyskinesia. The annualized tardive dyskinesia incidence according to a recent metaanalysis is 3.9% for second-generation antipsychotics and 5.5% for first-generation antipsychotics.[124] Tardive Dyskinesia correlate with higher mortality. If the methodological differences of the existing studies are taken into consideration the odd ratio (OR) lies between 1.4 and 2.2. It is unkown whether Tardive Dyskinesia are risk factor on its own or a surrogate for any unknown organic liability.[125]
Mortality through atypical neuroleptics is probably higher for those with an existing metabolic syndrome (approx. 50% of patients) than under typical neuroleptics.

Historical analysis of neuroleptic and treatment systems

So far there has been no evidence for an overall improvement in course of illness since neuroleptics have been introduced rather there seems to be a deterioration in the course of illness.

- A metaanalysis by **Hegarty et al 1994**[126] of 100 years of Schizophrenia treatment shows on the whole - if broader schizophrenia concepts are applied (i.e. duration of symptoms of more than 6 month before diagnosis is not required) a small variation of the proportion of markedly improved patients: 45% before 1925, 40% during the era of insulin coma, chemoconvulsive therapy and ECT (1926-1955), 48% after the introduction of neuroleptics (1955-1975) and 41% since 1974, that means 4 % below the quote of 1925 and the decades before. If more narrow diagnostic criteria are taken as a basis (Kraepelin) this metaanalysis shows an increase of the percentage of patients with substantial clinical improvement from 20% to 30%

since the introduction of neuroleptics. However the effects of improved treatment structures and psychosocial therapies between 1955 and 1975 are also included in this augmentation.

- In a separate metaanalysis with other cut of periods Warner[127] came to the result, that the outcome already considerably improved several years before the advent of neuroleptics through "dramatic postwar changes". He assumes an "effect of open door hospital movement, hospital milieu enhancement, work therapy, early discharge, vigorous rehabilition efforts and other reforms" after World War second.
- The observed improvement of outcome with the introduction of neuroleptics also occurs in comparison with the era of insulin coma, cardiazol shock and ECT, which also according to a longterm study by Ciompi & Müller showed "slightly significant worse tendencies in the course"[128] (translation V.A.) in comparison with the less invasive era before then.
- **Longterm follow up studies (over 22-32 years)** prior to the introduction of neuroleptics show **high recovery rates** 46 % – 68%, approx. 55% on average.[129]
- A Havard comparison study[130] compared a community oriented mental health hospital before the neuroleptics from 1947-52 with a community based mental health center from 1967-72 and found a higher readmission rate and greater social dependency in the second period. Under neuroleptics the former 7% long stay patients could be discharged.
- A systematic review (2006)[131] of 37 outcome studies of patients after their first schizophrenic oder schizo-affektive **psychotic episode** (all studies after 1980 with an average length of 3 years) comes to the following result: 42% of the 4100 patients show a good, 35% a moderate and 27% a bad outcome. Predictor of good outcome was additional psychosocial therapy. (Only with one exception there was obligatory use of neuroleptics in all studies.) Predictors of worse outcome were typical neuroleptics, presumably during this period in higher dosages. The duration of untreated psychosis had no impact on the treatment results. The authors assume, that the psychosocial interventions were of more importance. A progressive deterioration of the patients (i.e. an increase of bad treatment results in the course of the studies) could not be observed.
- There is distinctly better course of illness for first episode patients, diagnosed with schizophrenia in the third world where neuroleptics are hardly used (India, Nigeria, Columbia). After 5 years 63% of the patients in the third world had a good outcome compared to 37% of the patients in the develped world and also worse courses for the other patients.[132] Besides the minimal use of neuroleptics the role of social networks especially in India surely plays a central role[133]. An aspect that also played a central role in the Finnisch psychosis treatment model (see below).

The claim that dehospitalisation has only become possible through the use of neuroleptics is wrong.

- Dehospitalisation, in Great Britian started long before 1954 and showed no significant increase after the introduction of neuroleptics.
- In the USA dehospitalisation started to increase only between 1963 and 1978 as a result of fiscal decision making. Soon after an increase of hospitalisations started partly as a result of neuroleptics.[134]
- The Vermont Rehabilitation Study: only 25% of successfully released and rehabilitated patients continually took neuroleptics, 25% some of the time and 50% never[135].

Perspectives

For the next coming years no new pharmacological substances for the treatment of psychosis - acute and prophylactic - are available. Glutamatergic substances like **LY2140023** will not be available on the market before 2011[136]. Due to the high complexity and sensitivity of the glutamatergic system severe problems and new side effects are to be expected. Further, it is unlikely - based on there mechanism of action - that they can fully replace dopamine blocking neuroleptics. Consequently, it is not justified to stray away from new psychosocial treatment innovations in the hope of new substances.
In the face of the merely displaced side effects as a result of atypical neuroleptics and the failure to prove a significant improvement in the course of illness through the use of neuroleptics and because of a clear increase in mortailty as a result of neuroleptics a restricted use of neurolepticcs can be the only answer. Not neuroleptics but a specific and qualitatively good psychosocial treatment is the basis for treating psychoses. Neuroleptic treatment is only meaningful and helpful for a subgroup of patients (40 – 50%). Those patients that are treated without neuroleptics have a better functional and symptomatic outcome than under neuroleptic treatment[137] and no pharmacological side effects. Currently, the dominating treatment paradigm for psychotic people is mainly an unjustified biological one.

Steps towards a adequate/reasonable neuroleptic treatment

1. Awareness of the insufficient and harmful effects of current pharmacotherapy. At present there is enough evidence, to act according to the medical principle „**nihil nocere**" (do not harm) and to take measures that will protect patients. According to this principle one must act even if the evidence is sufficient but not yet complete.

2. Controling of somatic side effects

The following require special attention[138]: weight gain and obesity, diabetes, hyperlipidemia, QT-interval-prolongation in the ECG, increased prolactin levels and sexual side effects, extrapyramidal disorder, akathisia, tardive dyskinesia, cataract, myocarditis. To help reduce the long term side efffects for patients there has been an agreement to carry out the following tests regulary: Body-Mass-Index (+ hip circumference), plasma glucose level, lipid profile, prolactin increase aand sexual dysfunction, QTc measurement, signs of myocarditis for clozapine, signs of late dyskinesia, eye examination. These are to take place in relatively close intervals.

Tabelle 4.4a. Metabolische Untersuchungen unter Antipsychotikatherapie

Bestimmungen	Beginn	erste 4 Wochen	erste 3 Monate	alle 3 Monate	jährlich
Körpergewicht (BMI)	×	×	×	×	
Hüftumfang	×	×	×	×	
Blutdruck	×	×	×	×	
Nüchternserumglukose	×	×	×		×
Nüchternblutfette	×	×	×		×

(in Anlehnung an: Consensus Statement der American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity 2004)

Tabelle 4.4b. Weitere Kontrolluntersuchungen unter Antipsychotikatherapie

Bestimmungen	Beginn	erste 4 Wochen	erste 3 Monate	alle 3 Monate	halbjährlich
Blutbild [a]	×	×	×	×	
Kreatinin	×	×	×		×
Leberenzyme	×	×	×	×	
Blutdruck/Puls	×	×	×	×	×
EKG [b]	×	×			×
EEG (nur bei Clozapin/ Zotepin)	×		×		×

[a] unter Clozapin in den ersten 18 Wochen wöchentlich, danach monatlich, bei Thioridazin und trizyklischen Antipsychotika ebenfalls häufiger empfohlen

[b] unter Clozapin, Thioridazin, Pimozid, Perazin sowie Ziprasidon häufiger empfohlen

aus: S 3 Behandlungsleitlinie Schizophrenie (Kurzversion) der DGPPN.

3. Therapeutic consequences
In general the LDL cholesterol should be under **130** mg/dL, and for those at high risk like diabetes and those suffering from peripheral vascular disease LDL should be lower than **100** mg/dL.[139] Vaules that exceed these limits contribute to an increased mortality risk.

4. Minimizing combination therapies
There is no scientific evidence and completely insufficient data to justify combination theray in most cases. A combination of typical and atypical neuroleptics is generally not recommended under british NICE guidelines. Further, also a combination of atypicals increases the risk of mortality. There are currently only five double blind randomised controlled studies of combination therapy[140]: of clozapine with sulpiride[141], of clozapine with risperidone[142] and amisulpride[143]. It seems that after risk calculation there is only sufficient support for combination therapy using clozapine for those that show resistance to monotherapy. If tolerated it is only justifiable if there is no worsening of metabolic parameters. If there are no or unsufficient effects a return to monotherapy after 3 months is essential. Unfortunately this often does not take place. For insufficient response or contraindication for clozapine an effective combination treatment may be justified, if cardial, diabetic and metabolic parameters are not negatively effected and if the patient is recieving an observable clinically relevant lasting effect and all control examinations are carried out.

5. High dosages only with strict indication
There is hardly any therapeutic rational, unless one is presented with the fast metabolising gen polymorphism of the enzyme CYP P 450. In 2005 the Royal College of Psychiatrists in London published a report and summarized: *„The results of the published trials of high-dose antipsychotic medication for treatment-resistant schizophrenia provide no convincing evidence of efficacy*."[144]

6. Low dose medication (in an appropriate therapeutic milieu)
We can assume an average acute treatment dosage of 4+/-2 mg of haloperidol per day.[145] The individual dosage can vary around about factor 15. For patients recieving

neuroleptics for the first time the average threshold dose in haloperidol equivalents is with 2.0+/1 mg.[146]
Equivalent dosages to 2 mg haloperidol (= 100 mg chlorpromazine equivalents) are 2 mg risperidone, 5 mg olanzapine, 75 mg quetiapine, 60 mg ziprasidone und 7.5 mg aripiprazole.[147] No specific low dose medication studies with atypicals have been done so far.
Average when considered from a biological perspective just means that all individual are distributed around the mean value. Thus per definition then depending on the curve progression ca. 1/3 of the individuals will need significantly less than the average. Thus one should start from 1 mg haloperidol equivalent and slowly work up from there taking into consideration a delayed onset of effect of 10-60 days [148], so as to not end up administering an unjustifiably high dosage and to achieve least possible dosages of continuous medication. Likewise extrapyramidal motor, metabolic, neurodegenerative, neuroognitive, depressive und dsyphoric side effects[149] as well as the neuroleptic dependent mortality are directly and/or cumulative dose dependent. In one study there was a further significant symptom reduction under low dose treatment with haloperidol and risperidone after 8 weeks in 12% of the patients. Another study of first episode patients confirms this partially delayed symptom remission with an even later symptom reduction after 26-52 weeks (or even later) in more than 15% of the patients.[150]
Symptom remission is also substantially dependent on the psychosocial treatment.[151]
A temporary administration of lorazepam is often sensible and less harmful than a higher dose.
First episode projects using low dose treatment usually managed with **1,5 mg Haloperidol equivalent** (API - Finnland)[152], **2mg** haliperidol equivalent (Parachute-Sweden)[153] and 2mg risperidone (EPPIC - Melbourne)[154].

7. Laboratory test of CYP 450 polymorphisms
Neuroleptics and antidepressants are generally metabolised by single isoenzymes of the cytochrom P 450 systems (CYP450) in the liver. There is a genetically determined polymorphism for these isoenzymes**.**[155] The variability is partially responsible for the fact that the same medication in the same dose in different individuals can have differing treatment and side effects. By determining the individual polymorphism of these relevant isoenzymes (one time payment of approx. 730-950 €) one can determine the individual metabolic speed. For example, within the well studied CYP450-2D6 polymorphism which is relevant in the metabolisation of neuroleptics approx. 20% for caucasian populations are poor to very poor metabolizers. „**Poor Metabolizers**" need sufficiently less than 4mg of haloperidol i.e 2mg. To be a fast metabolisers (2-3% of caucasian population) can be one reason for treatment resistance. One can be surprised that these successes of pharmacogenetics are withheld from psychiatric patients and the general population.

8. Therapeutically guided reduction and withdrawl attempts[156]
They should only be attempted with medical supervision. A supporting social network is very helpful. Everyone who is potentially involved should be informed in advance. A crisis plan should be set up before starting and individual worries and fears should be discussed with professionals, in order to check how realistic they are. A dose reduction has to be slow e.g about 10% every 4-6 weeks. Further along in the dose reduction process it becomes sensible to make the dose levels smaller. The longer the medication has been taken, the more slowly one should proceed. For those that have been taking medication for more than 5 years reduction should be carried out over a 2 year period.

Those with multiple medications should always only reduce one substance and should always start with the one that is easiest to dispense with.
This process should only be started under stable psychological and social conditions. A daily journal should be kept possibly written together with a professional supervising the reduction. Healthy nutrition, fruits, lots of water, excercise, rest and lots of sleep after 23.00 (possibly valerian) are essential. No alcohol and no drugs, if possible no caffeine. Strong emotional reactions are to be expected and require support and possible creative outlets or possibilities of bodily abreaction by means of physical excercise. Possible psychological or physical abstinence symptom will quickly cease and change. If they are too pronounced then the reduction dose is too big. Then it is necessary to return to the last dose maybe even return to taking a bit more for a short while. Afterwards one should wait for 2-4 weeks or longer before starting another attempt and reducing the dose with a smaller amount. Every new dose level must be accompained with psycholgical stability before another reduction takes place. Short psychotic symptoms must not necessarily require a dose increase as a consequence. Stability can also be reached by other means. Supporting forms of psychosocial treatment can be relaxation techniques, the principles of recovery, coping techniques for those hearing voices, individual or group therapy, traditional chinese medicine.[157]
When faced with psychosocial instability it is important to start with close knit contacts 1 or 2 times a week to trusted therapeutic persons for evaluation. Often it is initially only possible to achieve a dose reduction to the minimal dose. Further long term therapeutic work though can lead to later further reductions or even discontinuation of neuroleptics in 25%-50% of cases[158]. Several attempts may be necessary[159]. Psychotic episodes after complete remission can – according to a pilot study[160] – be succesfully treated with diazepam in 50% of patients.

9. Forms of treatment avoiding neuroleptics for a subgroup of patients
Neuroleptics can not be meaningfully discussed outside of the **treatment context** in which they are used. Which dose and whether they should be used at all, is mainly dependent on the pharmacotherapeutic concept, the therapeutic milieu, the direct therapeutic work with the patients, the social context and timing. Hence **Soteria**-treatment ('being with' practice through the acute psychosis) and the so called need adapted treatment model from Finland (focused on work mainly with the families and social networks) and early intervention allow for good prospects of treatment without neuroleptics or with very low dosages i.e 1/3 to 1/5 of the usual dosages.

Under these terms there are 3 groups of acute first episode patients diagnosed schizophrenic or schizophreniform:
1. Pat, that do not require neuroleptics (**40%** - evtl. 60%[161])
2. Pat that benefit from neuroleptics (**40% -** evtl. 30%)
3. Pat, that only require neuroleptics for shorter intermittend periods (< 10%)
4. Pat, that do not show any reaction to neuroleptics, non-responders (**15% - 20%)**
For schizoaffective, delusional and brief psychotic disorders the options for neuroleptic free treatment in explorative studies is even much higher: 75 – 100% of patients. If they have to be taken then mostly only for a limited time.

Treatment without neuroleptics for a subgroup
The existence of a group of patients of about 40% of first episodes that do not require neuroleptics, has been proven in 9 studies since 1964 - 2 studies from the NIMH (USA) - spanning over two, five and recently even 15 years.[162] No study disproved this finding.

Also the placebo controlled medication studies for chlorpromazine showed a remission rate under placebo of nearly 40%, even in patient groups with multiple pretreatment with neuroleptics (Cochrane metaanalysis)[163].
Astonishingly since 1954 there have only been 7 randomised controlled studies on the problem of neuroleptic free treatment in first episode schizophrenic patients.[164] In 6 of these studies[165] neuroleptics are only used after careful and selective consideration. In all studies there is a group of 40% of patients (in one study 60%)[166] that have the same or better outcome depending on the intensity and duration of the accompanying psychosocial treatment by means of additional Soteria milieutherapy and/or a therapeutic work in and with the social network. These neuroleptic free patients have a significantly better treatment outcome as the matching control group under neuroleptics, without considering the side effects[167]. To decide whether patients belong to group 1., treatment contexts are required, in which patients can initially be without neuroleptics by choice for 3-6 weeks to allow sufficient time to be sure to what subgroup they belong to. Because of the described rapid secondary changes through the use of neuroleptics it is best for this patient group to not even start with neuroleptics. A 4-6 week delayed administration of neuroleptics under protective treatement conditions can not be considered detrimental or having a negative impact on prognosis for patient group 2. Overall the neurotoxicity of acute psychotic episodes is being refuted, especially for a relatively short duration and in a therapeutic setting.[168] Of course patients should always be allowed to start on neuroleptics at anytime if they choose. When neuroleptics are initially used for treatment, the group of patients that can successfully discontinue neuroleptics soon is 20%, i.e only half of the initial rate.[169]

9.1 Need adapted Treatment [170]

In several scandinavian treatment settings patients recieve a flexible family and network therapy and later an individual therapy if wanted or accepted (50% of the patients). In a crisis situation daily meetings can be arranged at home if necessary. In 2 studies qualified teams required an average of only 25-40 meetings over the course of five years. Mean Hospitalisation rates decreased to 42 or 17 days in 5 years.[171]

9.2 Soteria[172]

Soteria is a form of treatment for acute psychotic people in a small therapeutic community of 6-8 residents and the possibility of a 1:1 attendance through the psychotic experience, if needed. Neuroleptics are used only with a delay and thus selective and after mutual agreement.

9.3 Predictors of treatment without neuroleptics

Additonally there are established criteria for a successful neuroleptic free treatment in appropriate therapeutic contexts.
Following criteria are have been validated:

- Good age related psychosocial competence prior to illness[173]
  Exception: **not** in the need adapted treatment, i.e. the outcome is independent from this predictor
- late onset of illness[174]
- no psychiatric treatment of parents[175]

Symptom related criteria are:

- no speech disorders (i.e. " thought disorder")[176]
- rapid start of acute symptoms

Exception: this criterion was not valid within the neuroleptic free Soteria treatment and is not to be mixed up with the duration of symptoms that can be longer with equal results.[177]

Hence:

- the duration of untreated psychoses (DUP) was not a significant predictor[178]. Therefore a neuroleptic free treatment attempt is still justified after several months of acute symptomatology.

Only in some single studies the following positive predictors were observed:

- considerable precipitating events[179]
- absence of schizoid personality traits [180]
- death features with the psychotic experience[181]
- additional symptoms of an affective disorder[182]
- good family support network [183]
- a family system that allows for detachment [184]
- previous short psychotic episodes e.g. short hospitalisation [185]

10. Integration von adaptierter Traumatherapie

50% of all subjects diagnosed with a psychotic disorder have been sexually or physically abused during their childhood and adolescence.[186] In studies only for schizophrenia this rate is 45%. Emotional abuse, physical and emotional neglect have not been considered in these results. Patients seem to underreport or recall less.[187] There is a specific correlation in 20 studies to hallucination. Consequently an adequate integration of trauma therapeutic concepts and methods is essential as part of psychosis treatment.[188]

11. „Non-Compliance"

50% to 75% (e.g. CATIE)[189] of psychotic patients refuse medication medium-term (so called non-compliance). This is usually interpreted as a lack of insight into the illness. Often this is a consequences of warranted distrust in the information recieved.
Atypical neuroleptics inspite of what was initially expected and proclaimed have not changed the high rates of non-compliance. In the CATIE study withdrawal rate after 18 months were at 75%, some aytpicals show results worse than those for perphenazin. „**Compliance**"or treatment withdrawal is not a pure law of nature or a characteristic of the disease but essentially a reaction to the treatment options. In the finnish treatment models that incorporate family, social networks and selective neuroleptic treatment the compliance rate for first episode patients during a 5 year period was 18% (1.historic cohort) or 5% (2 % historic cohort).[190]

12. Non-Responder

Patients that are non-responders must be given the possibility to reduce or discontinue medication at the latest after having tried clozapine and possibly even a second neuroleptic. There is an urgent need for relevant randomised studies, that currently do not exist.

13. Treatment alternatives at choice

Patients must be put in a position where they can take as few neuroleptics as possible. The decision to take a potencially deadly medication can not be forced on the patient. Patients need to have options to choose from.[191] Exception should require legal verification for the restriction of choice.

15. Independent information

In Germany 2 billion euros per year is spend on pharma representatives, all of which comes from the profit made from the sale of different pharmaceuticals. How effective would an independent information system be with the same budget? There is enough money in the system coming from the medication paid for by the patients.

16. Independent research

In 1991 still 80% of the industry sponsored studies have been carried out by relatively independent researches at universities. In 2002 the pharmaceutical industrie did 80% of these studies by itself.[192]

Today 90 % of all psychopharmacological studies are financed by pharma industry.[193]

In contracts with the researchers the industry can insist, how the research is conducted, reported and which results will be published. The non-publishing of results is done systematically.[194] According to a review[195] in every study 50% of the results about effectivity and 65% of the results about side effects is published incomplete.

In 94% of all american and 80% of all britisch studies about atypicals the control group uses reference dosages that exceed the recommended dosage for these patients and often even exceeds that for severe cases.[196]

In 90 % of the studies of atypicals the drug of the sponsor is found to be the most effective. The result is called the „neuroleptic paradox": olanzapine beats risperidone, which beats quetiapine, which beats solian, which in turn beats olanzapine.[197]

In 2001 the editors of 12 leading medical journals jointly proclaimed that "the use of clinical trials primarily for marketing. . .makes a mockery of clinical investigation" and represents a betrayal of patients who participate in such trials altruistically.[198]

40% of the profit made from psychopharmaceuticals is spent on marketing and 10% of this budget is spent for opinion leader and opinion maker in the medical field.

2000 the expenditures for marketing of psychopharmaceuticals amounted 15,7Mrd. $.[199]

Also illegal practices increase. The monetary penalties or payments in settlement are exorbitant.[200]

These multiple deceptions because of marketing interests create a situation in which often neither reliable decision in clinical practice nor in healthcare policies can be made. The curent biological pharmacological research does not meet the demanded requirements, without relevant self realization of this issue.

The need for psychopharmacological research that is independent from pharmaindustry is evident in the light of this situation. What is needed are few but methodologically sound and longitudinal studies addressing most possible treatment relevant questions. In those control groups there has to be serious equivalent dosage for comparison. Furthermore, there is a need for comparison studies with selective neuroleptic and optimal psychosocial treatment. The approval of a new drug should be the beginning of independent so called phase 4 studies.

This is the only possibility of fullfilling the hippocratic principle of nihil nocere (do not harm).

Independent research can be achieved as shown by the examples of Standford and Yale. A strict behavioural codex prevents nearly all direct financial connections between industry and academic research. Exceptions might be „pool solutions" from financial contribution from pharma industry which allow for a independent support of the research. New solutions are not more expensive, money just has to be redistibuted. Users and their relatives must receive a critical control function in this research.

Fazit

The foundation for a good psychosis treatment has to be complex and based on a true psychosocial treatment model. In such a system neuroleptics must only be given selectively and in low dosages used only as a complement to psychosocial treatment when it is not sufficient in itself. For a successful implementation it is neccessary for existing treatment systems to change there focus to these central interventions. They must have priority.

The core interventions are as follows:

- working with the families and the extended social context from the start and throughout the treatment
- continuity of therapeutic relations (not only treatment continuity)
- low stimulus, trauma sensitive milieus with practice of 'being with' during psychosis
- individual therapy with individual indications
- support within the natural living environment and most possible normalisation
- psychotherapeutic competence of professionals
- earliest possible integration in education and profession

All further interventions are secondary to these. The rate of non use of neuroleptics or their dosages are ***one*** criterion for treatment quality.[201]

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