

## **Neuroleptics – Effects, Risks, Education and Treatment Contexts**

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What is the optimal treatment for first episode psychotic patients? Generally, almost without exception, the agreement among experts is to use neuroleptics as soon as possible and to keep patients on the medication for more than 2 years initially. Even though, more than 60% of the patients stop taking these medication independently, most of the psychiatric experts and their clinicians, influenced by these experts, have kept to this ground rule for the past 30 years and refer to many studies.

The recommended dosages are subject to historical changes, which hardly appear to represent any scientific rationality. The recommended attempt to discontinue medication after two and five years does not give consideration to the heterogeneity of the psychotic patient and it is usually doomed to failure. Basically, the non-compliant-patient is merely a few months ahead of this. What kind of consequences does this treatment strategy have for the patients? What alternatives and latitudes are there with optimal psychosocial treatment conditions? What can one say about it from a differentiated scientific and clinical perspective?

### **1. Consensus Guidelines**

Obviously experts continue to be united, as always.

But such general rules come with multiple problems.

#### Methodical problems:

The data is from group studies and is therefore not necessarily valid for the individual patient.

The study designs are often insufficient.

Short length of time of most studies

No or insufficient control groups after discontinuation of neuroleptics.

#### Historical errors (for whatever reasons)

Acute treatment with high doses of Haldol: 3x7mg up to 4x10mg of Haldol

Considering newer findings, which could have been found out many years ago, this form of treatment is to be considered as iatrogenic damage.

Who is responsible for the distorted and delayed information?

#### Selective experts

The experts are paradigmatic one sided and selectively put together.

The consensus decision is essentially defined by the paradigm of these experts.

There is no objective and clear database.

#### Bribery and corruption

Experts are influenced by the industry or get influenced and manipulated with financial benefits.

Example: Texas Medication Algorithm Project – currently Medicaid/Medicare is suing Johnson/Risperdal for damages. At least one expert received payments. Additional evidence from (already dismissed) officials about more bribes to other experts by other pharmaceutical companies as well.

Is trust in the professional guidelines justified?

**Guidelines are not a sufficient answer to the problem of the adequately supplied individual neuroleptic treatment. They are not neutral and are strictly empirically derived, but rather underlie the subjective opinions of selected experts, the created historical errors and are directly and indirectly influenced by the psycho-pharma industry.**

## 2. Compliance

More than 50% of the patients do not take their medication under regular treatment conditions or at least not as prescribed (Fenton et al 1997).

There is an equally high medication non-compliance- for physical illnesses.

Therefore the relapse rates are obviously equally high: 65% after one year, 80% after 2 years. *„Relapse rates of 65% at 1 year and over 80% by 2 years among drug discontinued or placebo substituted outpatients are also more accurate than the 53% relapse rate previously estimated (Hogarty et al 1998).”*

Even the atypical neuroleptics haven't changed anything about it, in contrast to earlier expectations and statements. This has been revealed since the CATIE study. Altogether the dropout rate after 18 months is around 75%, some atypicals are worse than the typical Perphenazine. Compliance or dropout is not a law of nature or a symptom of the illness, but essentially a reaction to the treatment that is offered. In the Finnish developed therapy models with family and social support networks and selective neuroleptic treatment the dropout rate for first episode psychotic patients over a time span of 5 years is around 18% (first historical cohort study) respectively 5% (second historical cohort study) (Seikkula et al 2006, pg.7).

**The willingness of patients to take neuroleptics continues to be minimal. For whatever reasons. Many years of developing and implementing psycho educational programs have changed nothing about it. There is a danger that depot neuroleptics once more are going to be made into an insufficient solution to the problem. It appears that to some clinicians it is the only answer to the CATIE study.**

## 3. Risks

### 3.1 Diabetes

Example Zyprexa:

At the end of 2006 secret Lilly documents were passed-on by an expert witness, hired by attorneys against Lilly, to the public interest law firm PsychRights. In subsequent NYT articles it was made public that since 1999 Eli Lilly had covered up alarming data regarding hypoglycemia and manifest diabetes after Olanzapine treatment.

Lilly now pays \$690 million to 8,000 diabetics as a result of a legal action and \$500 million to an additional 18,000 diabetic patients coupled with a sanction to keep quiet. An additional 1,200 claimants will likely follow. Considering the \$4.2 billion yearly sales of Zyprexa in 2005, this sum of compensation is hardly going to be felt by the company. The national and the international scientific evaluation systems as well as the public control systems have failed to effectively research a 7-year-old knowledge of a life shortening side effect and avoiding or minimizing it, even though it had been pointed out already in some studies and reviews. In the end it was up to the patients and the leaks in the pharmaceutical industry that created public awareness with the help of the media and at least started a legal battle.

Would this be possible with a high blood pressure medication as well?

### 3.2 Metabolic Syndrome – Cardiovascular Illnesses

Metabolic cardiovascular side effects:

Weight gain, raised lipid levels (reduced HDL), diabetes cardiomyopathy distinctly more with atypicals (i.e. Lieberman et al. AJP 2005)

The rates of weight gain are obviously considerably higher in naturalistic studies as opposed to industry dependent studies (McEvoy et al 2005).

A further rise in mortality as a consequence of these side effects is probable.

What does a weight gain of 3 kg in 4 weeks mean in the clinical every day life?

### **3.3 Neuroleptic Specific Mortality**

The treatment with neuroleptics (typical and atypical) is linked with a higher mortality.

A prospective Finnish study (Joukamaa et al 2006) over 17 years (only typical neuroleptic treatment) found – even after correcting cardiovascular illnesses, risk taking behavior like smoking and alcohol consumption, unnatural death – the total mortality rate increased by 2.25 times (95% CI 1.46-4.30) which is raised with the number of neuroleptics used in the following manner: the rate of mortality without neuroleptis hardly increased!

Number of Neuroleptics	Relative risk of mortality after matching confounding factors in comparison with the population	Confidence Interval
0	1.29	(95% CI 0.53- 3.11)
1	2.95	(95% CI 1.64- 5.38)
2	3.21	(95% CI 1.93- 5.95)
3	6.83	(95% CI 3.40-13.71)

<http://ahrp.org/risks/antipsychotic/joukamaa2006.pdf> (hyperlink for original article)

Probably sudden dysrhythmia (Torsades de Pointes – TdP) as a result of the QT interval (Witchel HJ, Hancox JC, Nutt DJ. 2003) (upper norm value 440ms, TdP risk from 500ms) are responsible for it, which is increased with higher dosages (Bralet MC, Yon V, Loas G, Noisette C 2000), however, even with average and low dosages occur minimally (Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. 2001). Even venous thrombosis with pulmonary embolism (Thomassen R, Vandenbroucke JP, Rosendaal FR, 2001) and asthma (Joseph KS, Blais L, Ernsr P, Suissa S, 1999) are suspected. QT interval extensions with TdP develop with antidepressants (tricyclic and tetracyclic antidepressants), NSMRI SSRI, Venlafaxine, Lithium (possibly through interaction with neuroleptics) and other internistic medication (i.e. antibiotics, antiarrhythmics, antihistamines).

A lot of atypicals can also extend the QT intervals. With most of them there is an additional increase of the cardiovascular risk factors (weight gain, hyperlipidemia, diabetes, cardiomyopathy), which in the Finnish study was taken as contingent on lifestyle and were therefore deducted in the study independent from neuroleptics<sup>1</sup>. Co-medication with anticholinergics appear to lower the risk of mortality (Waddington JL, Youssef Ha. 1998)

Earlier studies have already shown the increased mortality with neuroleptics. Waddington et al (1998): a study with 88 patients over 10 years showed raised mortality with increasing number of neuroleptics. Bratlet et al (2000) in a study over 8 years with 150 patients found the dosage of neuroleptics as the best predictor of mortality. Ray et al found (2001) through the retrospective evaluation of 481 744 Medicaid patients before the introduction of atypicals a correlation between neuroleptic dosage and sudden cardiac death. Montout et al (2003)

<sup>1</sup> This is only somewhat justified, because for example the neuroleptic induced deficit syndrom regarding lack of movement and the raised BMI raises this proportionately.

found in comparison with typicals additional increased mortality with atypicals, which Morgan et al (2003) verified.

These research results are not discussed enough within psychiatry and are not answered with concrete measures, even though they were already significantly publicized in 1997<sup>2</sup>.

With the handing out of medications with severe long-term side effects, decisions with potentially huge implications are made. In particular high dosages and combination therapies present a special risk. A pivotal way out is to avoid as much as possible and to minimize neuroleptic medication.

### **3.4 Combination treatments**

In light of this study one can only interpret the current increasing practice of multiple neuroleptical and anti-depressive-neuroleptical combination therapies as an especially high mortality risk for these patients.

Besides, it expands the spectrum of adverse reactions:

Typical + atypical = addition of severe side effects = TD + hyperlipidemia + diabetes + cardiovascular illness + neurodegeneration + mortality?

Atypical + atypical = more of the same?

Pharmacologically this is largely flying blind without instruments. Long time studies are missing.

### **3.5 Neurodegeneration**

Neuroleptics can lead to loss of cellular tissue (apoptosis), depending on the substance, dosage and length of time on the medication.

In a MRI-study Liebermann et al (2005) showed that under Haldol medication (up to max. 20mg daily) within less than 12 weeks a reduction of the gray matter takes place, especially in the prefrontal area, which amounts to 1.7% in one year and after 2 years 1.9% of the gray matter. The gray matter reduction under Olanzapine (up to 20mg daily) is completely disavowed in the abstract ('was not') and mentioned in the summary as -0.5% by the authors. And this is how it's done:

previously reported. The mean  $\pm$  SE maximum WBGM volume loss was  $-12.80 \pm 2.51$  cm<sup>3</sup>, or -1.9%, for the haloperidol group and  $-3.70 \pm 1.72$  cm<sup>3</sup>, or -0.5%, for the olanzapine group (Table 2). This magnitude of WBGM

(WBGM = whole brain gray matter)

The -12.80cm<sup>3</sup> of the Haldol group is the 2 year value, the -3.70 of the Olanzapine group is the 1 year value (in the second year the drop out rate was too high). Inherently this raises the difference in favor of Olanzapine.

ROI	Therapy	Week 52				Week 104		
		N	Mean (SE), cm <sup>3</sup>	P Value*	P Value†	N	Mean (SE), cm <sup>3</sup>	P Value*
WB	Olz	43	3.18 (2.73)	.16	.34	24	10.26 (4.04)	.78
	Hal	32	-9.81 (4.16)		.03	10	-3.32 (12.18)	
	Con	44	7.10 (5.41)					
WBGM	Olz	43	-3.70 (1.72)	.049	.03	24	0.91 (3.90)	.16
	Hal	32	-11.69 (3.41)		<.001	10	-12.80 (11.89)	
	Con	44	4.12 (3.64)					

The most distinct degeneration, however, was in the frontal lobes.

<sup>2</sup> Royal College of Psychiatrists (1997)

ies.<sup>8,9,13</sup> The mean±SE maximum WBGM volume decreases in our haloperidol-treated patients were predominantly seen in the frontal ( $-7.56 \pm 2.04 \text{ cm}^3$ , or  $-2.4\%$ ), parietal ( $-3.65 \pm 2.09 \text{ cm}^3$ , or  $-2.9\%$ ), and temporal ( $-1.33 \pm 2.56 \text{ cm}^3$ , or  $-1.1\%$ ) lobes, whereas little change was seen in the occipital lobes (Table 3). These

Unfortunately the rate of reduction for Olanzapine is not mentioned in the text.

One can gather it from the following chart, though.

ROI	Therapy	Week 52			
		N	Mean (SE), $\text{cm}^3$	P Value*	P Value†
FGM	Olz	43	-3.16 (1.21)	.15	.03
	Hal	32	-7.56 (2.04)		<.001
	Con	44	0.54 (1.78)		

The rate of the frontal lobe area after one year with  $-3.16 \text{ cm}^3 = 1\%$ <sup>3</sup> and is therefore **41.8%** of the Haldol effects, which, with  $-7.56 \text{ cm}^3$  equals 2.4% in this area.

For the patients treated with Haldol in this study a correlation is given between the reduction of the gray matter in the frontal lobe area and the slight improvement of neurocognitive abilities in the course of remission. For the group of patients treated with Olanzapine such specification is missing.

Both groups had been treated with neuroleptics up to 16 weeks prior. It's to be assumed that the neurodegeneration initially is the highest, hence the real extent is also presumably higher, in the Haldol group in terms of the whole gray matter  $12.80 (1.9\%) + 5.85 (=0.85\%) = 2.77\%$  on average after 2 years and 3 months of neuroleptic treatment with 2 psychotic episodes<sup>4</sup>.

At an average of  $12.80 \text{ cm}^3$  and a SE of  $11.89 \text{ cm}^3$  (at normal distribution) is in 16% of the cases after 2 years a reduction of more than  $1.9\% + 1.7\% = 3.6\%$  probable. The first episode inclusive with a SE of  $1.92 \text{ cm}^3 = 1.1\%$  after 12 weeks, in some cases even more than  $3.6\% + 1.1\% = 4.2\%$  after 2 ¼ years. Therefore one has to assume of the existence of a **special risk group**. An analog risk group is also calculated in the Olanzapine group for the frontal gray matter after one year at 1.4%, but because of dropouts nothing is available for the 2 year time frame.

	Reduction of the total Gr. Matter after 1 year	Reduction of the frontal Gr. Matter after 1 year	Risk group (16% = upper SE) Reduction of the Gr. Matter after 1 or 2 years (+ 3 months)
Hal	- 1.7 %	- 2.4 %	- 3.6 % (- 4.2 %) G.M. total (2Y)
Ola	- 0.5 % (= 29% of Hal-group)	- 1.0 % (= 42% of Hal-group)	- 1.4 % (? <sup>5</sup> ) G.M. frontal (1Y)

Further methodical shortcomings of the study cast the alleged difference between Haldol and Olanzapine into doubt and let the effect of the neurodegeneration appear uncertain.

- Higher Haldol dosages than Olanzapine dosages (max. dosage of both 20mg)
- Uncertain the medication was actually taken

The interpretation of the authors that Olanzapine would partly compensate a neurodegeneration effect of the psychosis itself appears to be unjustified, because the making

<sup>3</sup> The difference between the Olanzapine group and the control group is 0.98% in the frontal lobe area in comparison.

<sup>4</sup> In the Olanzapine group (in comparison to the Haldol group) in week 12 was initially a gain of the total gray matter and the frontal lobe gray matter measured. Therefore cumulative values are not to be calculated. Is this a short term neurogenesis/collateral branching or is it a swelling of tissue? Is this initial gain a functionally positive and the neurodegeneration a diminishing or a functionally inert, possibly even damaging process and therefore, though, the total degeneration a statistically distorted and diminishing effect?

<sup>5</sup> No additional effect could be calculated, because of initial swelling – see footnote 4)

of new pyramidal cells through SGA cannot be proven experimentally. Even neurotoxic effects of the psychosis are more and more questioned (McGlashan 2006b). What is basically methodically missing is a comparison group of patients that are not treated with neuroleptics. However, the research in the USA was extensively prevented (McGlashan 2006a).

Dorph-Petersen et al (2005) show on Macaque monkeys an overall reduction of approximately 20% of the gray and the white matter – mostly in the frontal and parietal lobe – after 17 – 27 months of neuroleptic treatment among with schizophrenia patients' comparable plasma levels on Haloperidol and Olanzapine. The effects on humans are likely a little less and more regional.

#### Open questions

- What are the long-term effects after 10 or 20 years?
- Are the patients informed today about this harmful aspect of neuroleptics, especially with Haldol? In the Haloperidol patient information leaflet I was not able to find any information regarding this.
- Why is Haldol still considered to be a legitimate neuroleptic in the field of acute psychiatry? The situation is even more complicated because other neuroleptics are not researched regarding their specific neurodegenerative effects.
- How is the neurotoxicity of other neuroleptics to be rated?
- Are studies being done regarding that?
- What does this mean for the published studies about the course of schizophrenia and the hypothesis of neurodegenerative tendencies of the mental suffering itself?
- Is the apparent improvement of the neuropsychological deficits by atypicals essentially an effect of lesser damage?

#### Wrong every-day models

In the clinical every-day magical, run-of-the-mill theories like “a lot helps a lot” appear to obstinately hang around. Powerlessness, impatience, but also not knowing is answered too quickly and with excessive pharmacological business dealings with fatal consequences for the patients.

**Patients are not really informed about all these aspects.**

**Justifiably so a high rate of medication refusal is feared.**

**Is it ethically responsible not to inform patients about it, even if it's only a suspicion?**

**The diabetes catastrophe<sup>6</sup> with Olanzapine raises many ethical questions.**

**Patients bear the whole risk**

**Thus patients are confronted with profound questions when taking the medication:**

- **Still unsatisfactory scientific results that can possibly prove to be fatal for them later on.**
- **Manipulatively kept secret information by the pharma-industry.**
- **Purposefully not sufficiently researched damages (neurodegeneration).**
- **Information not known by the psychiatrist.**
- **Psychiatrist does not reveal information.**

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<sup>6</sup> At present already 27.200 claimants in USA; \$1.19 billion compensation payments, facts Lilly has kept secret since 1999

How can a basic trust be developed like that?

Non-compliance is to be interpreted, from my point of view, as an apprehension to this uncertainty and as a legitimate mistrust.

High dosage treatments with neuroleptics, which for some patients ended in death even, should have been refused from today's point of view.

The subjectively felt side effects are frequently worse than the psychotic symptoms in the process. Ultimately the taking of neuroleptics arising out of an "insight into the disorder" often occurs under pressure or because of trust in the doctors and the medical team. If the trust is achieved through deception, the non-compliance rate will go up in the end. Also the extreme fears when psychotic are seldom reduced by insufficient education. A lot of patients can read between the lines. Only the hopelessness for want of alternatives forces most patients frequently to take neuroleptics in the end.

I see the first answer to the problem is a really open and participative approach to the neuroleptic problem.

Education cannot be avoided.

The patient has to have the final say in deciding her/himself about taking neuroleptics, at the very latest after the acute phase if the patient has been medicated without consent during such time to control dangerous behavior, which could not be controlled in a different way.

She/he must consider the effects, the risks, and one's readiness to assume the risks and the quality of life in order to decide.

There is a right to refuse neuroleptic treatment.

It's an aspect irrespective of the so-called 'insight into the disorder'.

(Vice versa some patients do take neuroleptics, even though they don't have the so-called 'insight into the disorder'.) Insight into the disorder is not a good explanation for the motivation to take medication, but a bad justification.

Insight into the disorder and the willingness to be treated are independent categories from each other and are extremely conditional on history and ideology.

Only then can compliance and refusal be overcome and perhaps a real concordance be reached.

Because the risks of the pharmacological therapy are not sufficiently assessed up to now, patients who do not want to take those risks must have alternative choices, therapeutic alternative choices where no neuroleptics have to be taken either, if the patients are not a danger to themselves or others. Psychiatry must also take on the commitment and the responsibility for the competent, professional setting of these alternatives. Choices of alternatives ought not to stay as private affairs, but have to be part of the complete treatment.

These alternatives have to be researched systematically and scientifically and provided with the care. (Ex)-User-organizations have demanded this for years.

When psychiatrists believe neuroleptics are necessary – which I regard in some cases as justified, even against the wish of the patient – they have to justify this judicially. If this method of verifying does not appear optimal, it has to be improved, but not replaced by the self-given power of psychiatry.

#### 4. Long term effectiveness of neuroleptics – long-term process

There is no evidence of improvement of schizophrenia in the long run through the treatment of neuroleptics.

1. “Essentially in the long run schizophrenia has not changed any despite of the effectiveness of antipsychotic medication in the treatment of acute psychoses and the drop in relapse.”

This was written by nobody less than Will Carpenter 1997.

2. Hegarty (1994) found in his Meta-analysis even a worsening between 1984 – 1994

3. Lausanne long-term study (Ciompi 1976)

289 registered patients (of 347 survivors from 1642 patients originally who between 1920 – 1962 were treated on psych wards with the diagnosis of schizophrenia)

The clinical cases showed:

Recovery 23% (29%)<sup>7</sup> + improved significantly: 17% (21%) = 40% (50%)

partial remission: 23% (29%)

grossly impaired: 16% (20%)

(uncertain cases: 21%)

The majority of the cases were neuroleptic free.

Only approximately 4% of the first time hospitalizations were put on neuroleptic in those days.

The total time of hospital stays under one year was for 47% of the participants and under 3 years for 43% (= 90%)

Approximately 50% ‘sure’ schizophrenics were hospitalized once only.

Approximately 2/3 of the 289 cases were hospitalized during less than 10% of the catamnesis period.

There were no clear-cut types of cases. To me that is a distinct indication of the sensibility for open ways of life and life experiences.

Also, patients with a very gradual start of chronic symptoms were able to attain complete recovery (15%) or improved significantly.

Other long-term studies (i.e. Bleuler, Harding (Vermont)) come to similar results:

Study	Sample Size	Average Length In Years	Subjects Recovered and/or Improved Significantly*
M. Bleuler (1972 a and b) Burghölzli, Zurich	208	23	53%-68%
Huber et al. (1975) Germany	502	22	57%
Ciompi & Müller (1976) Lausanne Investigations	289	37	53%
Tsuang et al. (1979) Iowa 500	186	35	46%
Harding et al. (1987 a & b) Vermont	269	32	62-68%
Ogawa et al. (1987) Japan	140	22.5	57%
DeSisto et al. (1995 a & b) Maine	269	35	49%

\*For schizophrenia subsamples

4. A better basic long-term result cannot be found with medication compliance either.

<sup>7</sup> Bracket = calculation without uncertain cases

- Around 40 % of the schizophrenic patients decompensate and become psychotic again even on neuroleptic medication after only one year following hospitalization:

*“A reappraisal of the literature suggests a 1-year, post-hospital, relapse rate of 40% on medication and a substantially higher rate among patients who live in stressful environments, rather than earlier estimates of 16%. (Hogarty u. a. 1998)”.*

- Andreasen et al 2005 found regarding neurocognitive deficits with 84 study patients who had been treated optimally over more than 10 years with medication (no information about the kind of neuroleptics), between the 5<sup>th</sup> and the 9<sup>th</sup> year of the observed course a significant deterioration of the neurocognitive achievement parameter, verbal memory and problem solving abilities as well as language and motor skills. According to the older long-term studies (McGlashan 1988, McGlashan et al 1993, Harding et al 1987a, Harding et al 1987b) one would have expected a stabilization after the 5<sup>th</sup> year.<sup>8</sup> A different 10 year course study (Hoff et al 2005b) with 21 schizophrenic patients (13 atypical, 3 typical, 3 only Lithium, 2 without medication) found, however, no deterioration of neuropsychological parameter, even though – in contradiction to this – the same working group referring to the verbal learning published in a congress-abstract a deterioration (Hoff et al 2005a). In a two-year study of first episode schizophrenic patients Albus et al (2002) report, not in the evaluation, yet briefly in the discussion about a marked negative effect of the neuroleptic medication on the visual memory, on the visual motor processing, on the attention span as well as on the abstraction/flexibility. With patients, who were not on neuroleptics (who discontinued taking neuroleptics on their own accord weeks or months before the research), hardly any deficits were found. Their abilities were close to the level of the control group.<sup>9</sup>
  - And what about atypical NL?  
As far as I know there are no studies regarding the long-term effects of atypicals after 5 – 10 years. This is astounding since most of the atypicals have been on the market for more than 8 – 10 years. Normally one knows of the necessity of such studies on the day of the initial release of what appears to be an important medication.
5. NIMH stampedes right up front for the neuroleptic treatment in spite of this situation of poor treatment results. It defines schizophrenia as chronic and debilitating contrary to historical evidence.

*“Schizophrenia is a chronic, severe, and disabling brain disorder that affects about 1 percent of people all over the world.”* <http://www.nimh.nih.gov>

**In contrast to today’s frequent opinion that neuroleptics are the essence in schizophrenia treatment, this cannot be proven because of long-term studies as well as historical comparison studies. The margin of non-medication is obviously considerably larger than many professionals believe. Even if not much more happens than the**

<sup>8</sup> McGlashan (2006a) quote: „The long-term (9- and 10-year) outcome data emerging from 2 well treated, first-episode sample (suggest that deterioration in schizophrenia does not plateau as seen in older, long-term follow-up patient samples where exposure to medication was absent or intermittent.“

<sup>9</sup> This last finding is not in the Albus et al 2002 publication, but in Dose 2002 as an advance notice of the than handed in publication. The publication observed, that the medication was not controlled.

**custodial psychiatry of the 60's in Switzerland, this will lead – measuring the long-term prognosis – to no worse treatment results.**

### **5. Atypicals are not effective to be curative either**

but by means of postsynaptic D2 blockade with different consequences.

- Newer PET-scan studies<sup>10</sup> show that patients diagnosed with schizophrenia a normal D2 receptor number is existent.
- Only during the acute psychosis is there a phasic<sup>11</sup> raised presynaptic dopamine distribution. It ends with the remission of the acute psychosis. Around 70% of the “schizophrenic“ psychoses are of episodic nature.
- Neuroleptics block the receptor postsynaptic, even when the phasic raised dopamine distribution is normal again. Dosages, that block more than 65 % of the dopamine receptors, lead to producing or rather strengthening side effects like EPS and hyperprolactinaemia, so-called negative-symptomatic (deficit-syndrome) and of neuropsychological deficits (and other known side-effects), since the dopaminergic system regulates attention, drive, motivation, emotions and values.
- If the dopamine receptors are blocked by neuroleptics within weeks there will be a compensatory counter regulation, in that new receptors (up-regulation) and collaterals of the nerve endings are established.<sup>12</sup>

This causes the dopaminergic level to increase and the development of symptoms or relapses is in part lessened and intensified.

Clinically this is apparent in the usually more severe symptom characteristic of the 2<sup>nd</sup> treated psychosis with increasing tendency to a combination of several atypicals and/or typicals and the patient's difficulty to come off neuroleptics (rebound) after having taken them for a long time. In my view, this is to be taken as a limited tolerance development towards the neuroleptic drug. Therefore we have to assume the high frequency of recidivism at premature or prescribed attempts to stop the medication is still an unknown percentage of an effect of the neuroleptic drug itself. The revolving door effect of modern psychiatry in comparison with i.e. the Lausanne study makes this very clear.

- Medication studies that include patients in the so-called placebo group shortly after discontinuing neuroleptics, establish therefore distorted higher relapses without neuroleptics.
- However positive-symptoms also develop as a result of non-dopaminergic mechanisms (Laruelle 2000). Only 30 % of the variance of productive symptoms can be interpreted as dopaminergic mechanism (Laruelle 2000). Presumably because of that 25% of the acute psychotic patients are under the regular D2 blocking neuroleptics therapy-resistant (Schäfer et al 2004) and others partial.
- Some patients have a lasting prefrontal hypodopaminergic condition at the D1 receptors, which are prevalent there. This is even further affected by neuroleptics that not only block the D2, but the D1 receptors as well. This has negative consequences for neuropsychological functions (i.e. functional memory).
- It can be assumed of an average dose of 4 +/- 2mg Haloperidol daily. (Mc Evoy 1991) The individual dose can vary around the factor 30. With patients treated with neuroleptics for the first time the average threshold doses of Haloperidol with 2.0 mg are again almost half as low (Kapur 1996). The average always means in biological

<sup>10</sup> z.B. Farde u.a. 1990, Nordstrom et al 1995, Martinot u.a. 1990, Laakso et al 2000.

<sup>11</sup> Laruelle et al 1999, Breier et al 1997, Abi-Dargham et al 1999, Abi-Dargham et al 2000.

<sup>12</sup> Baldessarini & Tarsy 1980, Abi-Dargham et al 1999, Heinz 2000

contexts, that the individuals are in and around that mark. By definition approximately 1/3 of the individuals then need considerably less than the average depending on the curve progression. Therefore we should slowly tritrate up from 1 mg Haldol equivalent (latency of effect 10-14 days, + temporarily Lorazepam), to not overdose that group of patients.

- Neuroleptics and antidepressants are metabolized in the liver with several isoenzymes of the Cytochrome P 450 enzymes (CYP450). There is a polymorphisms for these isoenzymes induced by genetics. This variability is among other things responsible for fact that a medication with the same dose shows very different effects with different people, not only regarding the main effects, but also the side effects. Because of the disposition of the individual polymorphisms of this relevant isoenzyme (one time costs around. 730-950 €) the individual metabolizing speed can be determined. For example, for the well researched and for the reduction of neuroleptics central CYP450-2D6-polymorphisms, around 20% of the Caucasian population are slow or very slow metabolizers<sup>13</sup>. „Poor metabolizers“ clearly need less than 4mg or, as the case may, be 2mg Haldol. Additionally significant for the neuroleptics-metabolism is the isoenzyme Cyp450: 2C19 und 1A2. The other way around ultra-fast metabolizing can be reason for therapy resistance. (Presumably there are even further, likely not dopaminergic mechanisms with acute psychoses.) I am surprised that these results of the pharmaco-genetics are withheld from psychiatry patients and everybody else. This would be a genetic aspect that would be very beneficial for them.
- First episode psychotic patients treated with low dosage generally manage with 1.5 mg Haldol-equivalent (API Finland), 2 mg Haldol-equivalent (Parachute Schweden) or 2mg Risperidon (Eppic Australia - McGorry et al. 1996).
- Chronic blockade of the dopamin-receptors and neurodegeneration weaken attention, drive, motivation, emotions and developing of “meaning“, the functions of the dopaminergic systems. Therefore biologically patients can only learn with limitations or not at all, mentally and socially.

**Short-phased psychotic breakdowns (which also depends on psychosocial factors) basically don't have to be treated with neuroleptics provided there is a good psychosocial treatment (Soteria and/or NATM) in place.**

**Besides the physical side effects, neuroleptics generate unwanted dopaminergic effects that negatively influence the course of the psychotic breakdowns. Often neuroleptics raise the recidivism rate as well as intensify the symptoms after discontinuation (which regularly is to be expected). This can only be prevented by long term D2-blockade (life long neuroleptic treatment) for the price of a deficit syndrome and of neuro-degenerative, metabolic and other side effects.**

**Another reason to basically minimize the use of neuroleptics, especially regarding the dosage.**

**This is accomplished by good complementary and substituting psychosocial treatments.**

## **5. Benefits-Cost-Analyses Effectiveness**

Example: atypicals

Finally after 10 years of marketing authorization we now have the first study of its effectiveness (Rosenheck et al 2006). It was systematically delayed. Even Lieberman expressed that.

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<sup>13</sup> Schwab et al 2002 ; de Leon et al 2006

For the prescription of atypicals the US health system pays an additional \$10 billion (10,000,000,000), without achieving an overall standard of treatment progress with psychotic episodes.

In Germany the extra costs per patient in 18 months are 14.000 €

Finally in an additional study the side effects are suppose to be researched, which likely will take 3-5 years and is financed by NIMH. Until then the patent protection of 15 years for the most important products like Zyprexa, Risperdal and Quetiapine (90% of the US-market) will be over and therefore likely the economic goal achieved. And for the time being every substantial restriction or every ban initiative is likely to be prevented with reference to the result of the study. For example 30% of Lilly's revenue is through the sale of Zyprexa®, and will go to any lengths to oppose a ban.

Who may and can decide what \$10 billion are spent for in a national health system?

However, 90 % of the studies are done by the pharmaceutical industry and the industry decides the contents of the research. This is documented in a report of the British House of Commons<sup>14</sup>.

But clinicians depend on them if they don't want to give in to every innovation. Other studies are not conducted. Public money is not available for that.

In Germany 17000 pharmaceutical representatives work with 25 million doctor contacts per year. The cost for that is 2 billion euros and is financially carried by the price for the medication. Would it be possible and necessary for example to have a public and independent pharmacological information system, in which 17.000 employees work and are paid by health insurances or the entire medical fraternity?

In other words: on average 40% of the price for medication are proportionate marketing costs that are only possible if this kind of marketing is allowed.

**The necessity of a psychopharmacological research independent from the pharmaceutical industry is evident because of the decade long situation. Patients ought to have a critical function in the research and care as well.**

**On top of that an extensive and independent information system is to be demanded.**

## **6. Optimal practice with neuroleptic therapy.**

Generally it ought to be considered to have optimal treatment conditions in order to not even start a therapy with neuroleptics.

Possibilities of the optimal gradual discontinuation of prophylactic neuroleptic therapy under individual optimal psychosocial care haven't ever been scientifically researched since the introduction of neuroleptics. They certainly do exist. This we know especially from reports of individual cases, the so-called 'non-compliant'-patients. Therapy programs geared towards recovery (Amering & Schmolke 2007) could open more possibilities.

How can one proceed with a first episode psychotic person?

### **6.1 Does one have to prescribe neuroleptics right away?**

Absolutely not!

#### **6.1.1 Randomized controlled studies of first episode psychotic people diagnosed with schizophrenia**

Meta-analysis Bola (2006)

There are only 6 (!!) randomized controlled studies of first episode psychotic patients diagnosed as 'schizophrenic' with a control group of unspecified milieu-therapy and delayed

<sup>14</sup> <http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf>

and selective neuroleptic prescription since the introduction of neuroleptics (1954). In 5 of these studies, in which initially for 2-6 weeks no neuroleptics were given and after that 40% of the cases continued to be treated without neuroleptics, the outcome was in the experimental group (with delayed and then selective neuroleptic treatment with approximately 60% of the patients) only slightly better. Patients, that could be treated entirely without neuroleptics because after an initial neuroleptic free treatment span of 3-6 weeks (more likely limited to 4 weeks of Diazepam or Lorazepam) were adequately remitted, henceforth neuroleptic medication was entirely abstained from, always belonged to the group with the best treatment results (Schooler et al 1967; Rappaport et al 1978; Bola & Mosher 2003; Ciompi et al 1993; Lehtinen et al 2000).

### **6.1.2 DUP studies:**

Whether the duration of the untreated psychosis (DUP) has an effect on the outcome is controversial. There is much to be said against it, especially if one rightly does not count the group of patients with one-time episodes. Yet, this is done with DUP intervals under 6 months, which is misleading and therefore the statistical effects can be seen.

It's important to note the therapeutic shortening of the DUP through early intervention.

#### Study de Haan et al (2003):

Not the duration of the untreated psychosis is decisive for the outcome, but the DIPT (delay of intensive psychosocial treatment) is.

So far there is not a single study, which proves that the pharmacological shortening of the DUP has positive effects on the medium and long term course of the symptoms of psychoses (Craig et al 2004, Garety et al 2006, Kuipers et al 2004, Marshall & Rathbone 2006, Larsen et al 2006).

Even the neurotoxicity of psychoses is not proven. More and more known experts do doubt it (i.e. Craig et al 2000; Ho et al 2003; McGlashan 2006b) The Meta-analysis by Wyatt 1991 hypothetically purporting this has many methodical shortcomings (Carpenter 1997) and has to be newly interpreted within the scope of new findings in regards to neurodegenerative effects of neuroleptics, especially typical neuroleptics (Lieberman et al 2005a).

## **6.2 Does every so-called schizophrenic psychosis need neuroleptics?**

**No, it does not.**

It depends on what the acute accompanying and other psychosocial treatment look like.

### **6.2.1 Need-adapted treatment model:** (Alanen 2001; Aderhold et al 2003)

Right from the start flexible, accompanying family and social support network therapy and later selective (50%) individual therapy, daily in an acute situation in the beginning, totaling on average of 25-50 sessions over the course of 5 years.

#### Integrated treatment of acute psychosis project (API) (Lehtinen et al 2000):

Altogether 67 first psychotic episode cases and out of that 33 schizophrenic and 11 schizophreniform diagnosed people, multi-center-study. Treatment over 2 years: 43 % of the schizophrenic as well as the schizophreniform diagnosed subgroup continuously treated without NL. DUP, premorbid functioning, amount of the psychotic symptoms and diagnoses were **no** predictors for a successful treatment free of neuroleptics. Significant better result of the neuroleptic free group as opposed to the NL treated patients and the experimental group in comparison with the control group (duration of the hospital treatment, amount of symptom free patients, psychosocial functioning (GAS)).

#### Open Dialogue Approach in Acute Psychosis Project (ODAP) (Seikkula et al 2006):

34 first episode psychotic people were recruited in the API-cohort (historical comparison group) and later 46 first episode psychotic patients in the ODAP cohort (diagnoses: 26% schizophreniform psychosis, 38 % schizophrenia, 15 % acute temporary psychosis, 21 % not otherwise classifiable psychosis) were recruited.

The treatment was over **5 years**. Only 29 % of the ODAP patients were actually treated with neuroleptics during the 5-year time span, 26 % right from the beginning and 17 % constantly over the 5 years.

In the subgroup of the schizophrenic or the schizophreniform diagnosed 62% were never treated with neuroleptics + 8% occasionally treated with NL + 30 % continuously treated with NL.

This cohort was compared with an earlier historical cohort from the API-study in the same region.

### Compilation of the most important findings:

	API N=33	OD N=42	Diff
<b>5 year results</b>			
	Recruiting time	Recruiting time	API
	4/92 -12/93	1/94 -12/97	OD
DUP	4.2 months	3.3 months	s.
Discontinuation of therapy	18 %	5 %	s.
Hospitalization in 5 years	42 days	17 days	s.
Relapses: 1 or more within 5 years	39 %	29 %	ns.
Neuroleptics	after 5 y: 24 %	After 5 y: 17%	
All first episode psychotic patients	total: 39 % over 5 years	total: 29 % over 5 years	ns.
No residual symptoms	76 %	82 %	ns.
In employment or university	70 %	76 %	ns.
Unemployed	12 %	13 %	ns.
„Disability allowance“ = unemployed or on pension	27 %	14 %	ns.
Individual therapy	42 %	46 %	ns.
Therapy meetings with the social network	37 times	24 times	ns.

The treatment teams are very competent in this region after all these years and are able to work, if needed, on an ongoing basis with the patients and their family over the course of 5 years. Under these conditions the functional outcome was improved, the DUP and the rate of hospitalization, the therapy dropout rate and the number of patients treated with neuroleptics significantly, or consequently, lowered.

### 6.2.2 Soteria

When treatment was supplemented with intensive milieu-therapy (being with + reintegration), there was an additional positive treatment effect in the randomized control-group comparison of medium effect size, and even of higher effect size for the subgroup of ‘schizophrenic’ people with gradual start of symptoms.

Over 2 years 42 % of all the patients were continuously without neuroleptics, the same percentage even in the group with gradual start of symptoms, which is generally considered difficult to treat.

Neuroleptic rate in 2 Soteria-cohorts			
	6 <sup>th</sup> Week	Discharge	After 2 Years
Cohort 1 (1971-1976)	9 % NL	19 % NL	58 % NL
Cohort 2 (1976-1982)	25 % NL	59 % NL	58 % NL

The environment of regular acute care units leads to 3-5 times higher neuroleptic dosages contrary than a relaxed environment (Ciompi 1993).

On top of that acute hospitalizations can traumatize relatively frequently (40 % in McGorry 1991)

Soteria-elements in acute care units can lead to a reduction of restraints of 80-90% (Jiko 1997).

What is conducive to real recovery?

How often are therapies offered, that are only an add-on, where as the actual therapeutic core element is absent?

### **7. What to do? Course of action with a first episode psychotic person, to some extent even with multi-psychotic people:**

Establish trust and safety.

A traumatic experience may have occurred. Every intervention is to be trauma-sensitive and retraumatization is to be avoided. Maximum transparency and control of the events by the patient

Thus it is important, early on, to ask appropriate questions regarding traumas and possible contact with the perpetrator (even if indirect).

The work with the family and the social network right from the start presents the most important intervention from which all the following treatment plans result.

Soteria would be an excellent option, should the outpatient setting not be enough.

Do take your time prescribing neuroleptics, easily for 2-3-6 weeks.

Psychoses often abate naturally even without neuroleptics (see long term studies).

Neuroleptics are only needed, if there is no improvements of the symptoms in a well thought out overall therapeutic context or the problem is that the person is a danger to him/herself and/or others.

If the need of a neuroleptic treatment arises, first the pros and cons ought to be discussed in possibly 2 family or social network meetings. Everybody should be positive about this attempt. Sometime alternative ideas come into being.

Initially one can even use neuroleptics for a short-term.

There are pharmacological alternatives:

Carpenter et al (1999): 50% of the relapses in an interval of an experimental group in full remission were treatable well and adequately with a mono-therapy of Diazepam without inducing dependence.

When taking neuroleptics try to discontinue them soon after the remission.

If this does not work, neuroleptics in low dosages should be prescribed.

They really do not **heal** the psychosis, but help to suppress the otherwise unbearable symptoms.

Work, possibly right from the beginning, with the first episode psychotic patient with the help of the ongoing and meaningful family system and social network and continuing if there is a need over 5 years, possibly even longer.

Individual therapy with patients, who are already relatively independent (approx. 50%)

Cognitive and behavioral therapy in case of persistent hallucinations

I can only advise patients: Find yourself a therapist who believes in you and whom you can believe and trust! Keep looking if you have not yet found one.

A group of patients diagnosed with schizophrenia for whom neuroleptics present the best possible compromise will remain. It is likely 30% and 40% with optimal psychosocial treatment and is a result of the percentage of people in remission without neuroleptics on the one hand and the true non-responders to neuroleptics on the other hand. For other patient groups with psychotic symptoms (acute and transient disorder, delusional disorders, schizoaffective disorders) the percentage of meaningful neuroleptic prescription with appropriate psychosocial treatment could considerably be lower, possibly be even zero (Lehtinen et al 2000, Seikkula et al 2006).

The move to neuroleptic treatment would be easier for these patients the more believable the efforts of the psychosocial therapy are. I believe that the so-called compliance problem would then take a back seat.

There will be a patient group that shows relative constant productive symptoms, but who are not helped by neuroleptics whatsoever, yet their life shortened: 10-15 %. Who's looking for alternative forms of care and finances them adequately?

**There is ample room before making use of neuroleptic therapy, much larger than is generally claimed these days.**

**The room grows larger with good and continued (5 years) psychosocial therapies.**

**Working with the family and the social context, selective individual therapy and good milieu-therapy are central therapy elements.**

### **8. Problem with prodromal early intervention**

The current knowledge and therapeutic mechanism of NL does not justify the usage of neuroleptics. However such an early treatment in the prodromal stage would have fatal consequences. Approximately 5 % of the population hears voices (i.e. van Os et al 2001) and up to 30% of the population have transient psychotic symptoms, according to the research of the Institute of Psychiatry, Kings College London in 2006 (Freeman et al 2006)<sup>15</sup>.

Even if one defines a high-risk profile of so called prodromal patients, even they only have a conversion rate to psychosis of 40% in one year (Yung et al 2003, Klaasen et al 2006).

Patients without a real risk of psychosis would therefore inevitably be treated. Wrong positive prognoses and treatments are currently not avoided.

Early intervention would needlessly treat not only the people with harmless psychotic symptoms (15% of the population) with neuroleptics, but also patients with incipient short-lived psychotic episodes and single schizophreniform episodes and the severity of their disorder would unpredictable.

It is also completely unclear, what is supposed to happen after discontinuation of neuroleptics. The vulnerability remains and the possibility of a relapse might be even higher after a neuroleptical treatment (McGlashan 2006).

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<sup>15</sup> <http://www.iop.kcl.ac.uk/apps/paranoidthoughts/information/common.html>  
<http://www.medicalnewstoday.com/medicalnews.php?newsid=45931>

The extent of wrong positive (that is: not needed, wrongly administered) treatments already within stringent studies and even more so in the open clinical application would be enormous. The additional follow-up costs, because of long-term somatic side effects and additional brain lesions, are inconceivable.

A research project in Manchester, the EDIE-study (Morrison et al 2004), could back up that a strictly individual psychotherapeutic intervention (CBT) is very effective, yet cannot prevent the transition to distinct psychosis.

All the other prevention studies use neuroleptics, yet have amazingly higher transition rates to psychosis than in the EDIE-study. One of these studies, the prime-study at Yale for the prevention of psychosis of high risk patients, which used only neuroleptics (Zyprexa®, sponsored by Lilly), was cut short after the number of transition to psychosis in the treatment group and the control group with placebos was not significantly different, 58% of the patients within a year (original length of study 2 years) already refused to take the neuroleptics and some of them sued the researchers for missing information regarding the diagnostic uncertainties of the approach and the side effects of the medication<sup>16</sup>.

Purely psychosocial prevention programs are not implemented however. The development of newer treatment models is mostly in the hands of universities, which are as shown not independent and follow their own economic interests.

Early detection means from the perspective of the pharma-industry means broadening of the range of indications and therefore more sales and profit.

Prevention is first of all the domain of the psychosocial interventions.

A study of flexible family therapy and possible complementary individual therapy has not yet been done anywhere worldwide, even though this model of therapy would be very appropriate in view of the psychosocial predicament of the target group (detachment from parents). Not until it's proven that good psychosocial intervention is ineffective, are medical intervention studies of high-risk groups even justified. Even then it is not to be expected that the long-term prognoses improve by this kind of intervention. More likely the opposite will be the case.

### **8.1 Alternatives in early diagnosis**

In Stockholm a project was started over a year ago, at which employees of the welfare board, of child and youth psychiatry and of adult psychiatry do dialog/review-therapy with youths who subjectively experienced problems, independent of possible disorder symptoms, together with the whole family and any others the person is close to. Such an intervention model likely would not be researched at any German university. Third-party funds by the pharmaceutical industry would not be available and I don't believe for example that the DFG (German Research Center) would approve funds either. As far as I am concerned, considering the dominant biological psychiatric paradigm, no psychiatric field of any German university would show any interest in that.

**No early detection programs, which use psychotropics, as long as psychosocial intervention models are not proven to be ineffective. The effectiveness of psychosocial intervention is to be advanced with public money. First choice with youth and young adults are family- and network therapies.**

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<sup>16</sup> <http://www.ahrp.org/cms/content/view/157/80/>

## **9. Can the overall situation be changed?**

### **9.1 Psychiatry as a science**

Psychiatry ought to develop the purpose of an interdisciplinary and integrated social science again. Psychiatrist ought to be experts for complex bio-psychosocial overall situations and problems.

Psychiatry faculties that do justice to a humanistic integrative and interdisciplinary orientation of the profession in the fundamental- and treatment research

Reestablishing the independence of psychiatry as a science.

### **9.2 Pharmacological research**

Strictly keeping pharmaceutical industry, care services and research separate.

Establishing an effective, yet independent of the pharmaceutical industry, care research with the participation of the patients and their family with complete transparency of the data for the protection of the patients.

### **9.3 Psychosocial treatment research**

Publicly funded studies as well as publicly funded models of optimal psychosocial treatment without or with minimal pharmacological therapy, because there is a great lack of it and a great interest by the patients.

The study protocol ought to include comparison groups, which are not or minimally pharmacologically treated, yet are optimally treated psychosocially and the evaluation of therapy studies.

### **9.4 Psychiatric care**

Establishment of therapeutic choices for the patients especially in order to avoid or minimize psychopharmacological treatment.

Public funds for innovative psychosocial projects in co-operation with the patients and their family members

Promotion of implementation of Soteria-facilities and outpatient treatment teams with systemic orientation.

### **9.5 Involvement of the patients and their family members**

Have a say and control by the patients and their relatives on every relevant level.

Qualification programs for and by patients to become experts from their own experience (peer experts) in the treatment of others as well.

## Evaluation projects for personal budget: patient participation about the utilization of the allocated funds.

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