A Guide to Minimal Use of Neuroleptics: Why and How

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Table of Contents

Tables and Figures

Preamble

In preparing this review, we are hoping that it will encourage people to become actively engaged with the use of neuroleptics in the treatment of individuals experiencing psychotic symptoms. Overall, it represents a critical discourse concerning the use of these medications and their indications, as well as any problems associated with them. These perspectives are embedded in a scientific context to emphasize that this is not an ideological discussion, but rather an attempt to promote scientifically founded decisions on the behalf of clients. Consequently, a key portion of this contribution addresses the issue of "What to do?" Responding to patients' needs means finding ways of utilizing these medications that offer the greatest benefits, with the fewest possible unwanted effects, for individuals experiencing psychoses. In addition, it deals with the ways in which neuroleptics can be most effectively and reasonably combined with other interventions. The aim of treatment is always to keep patients' well being in mind.

Since we hope that the readership of this review will include lay readers as well as those considered "experts" or "methodologists," we have chosen to define many technical terms in the text. We have provided references for the scientific material that is being citied, with a full listing of references at the end of the text.

1. Theoretical background: The dopamine hypothesis of "schizophrenia"

The dopamine hypothesis of "schizophrenia" has been around for over 50 years, and has been revised and explicated repeatedly (Howes & Kapur, 2009). The current state of research suggests that psychotic experiences as part of an acute psychosis (so-called schizophrenic and schizoaffective disorders), and even mild psychotic features in individuals with a high risk for full-blown psychosis, are associated with an increase in presynaptic dopamine production and release in the ventral corpus striatum, an area below the cerebrum (Fusar-Poli et al., 2013a, 2013b).

These changes are considered to be the somatic basis for transformed environmental perceptions, such as the overstimulation of sensory organs, and the seeking of explanations for these unexpected experiences. This may be followed by delusional thinking and hallucinations that are related to earlier (and often traumatic) life-experiences and beliefs (Heinz et al., 2010; Winton-Brown et al., 2014). In atypical forms of "schizophrenia" without overtly psychotic phenomena (i.e. without "positive symptoms," see below), such over-activity in these brain areas is not found. In cases of mania or depression with psychotic features, changes in dopaminergic transmission have not been demonstrated to date (Winton-Brown et al., 2014).

All activity of the brain relies on stimuli that spread in particular areas across switching points (synapses) through the use of neurotransmitters (e.g. dopamine). The arriving stimulus is called "presynaptic," while the proceeding part of the synapse is called the "post-synaptic receptor."

The following image illustrates the transfer of signals at the synapse:

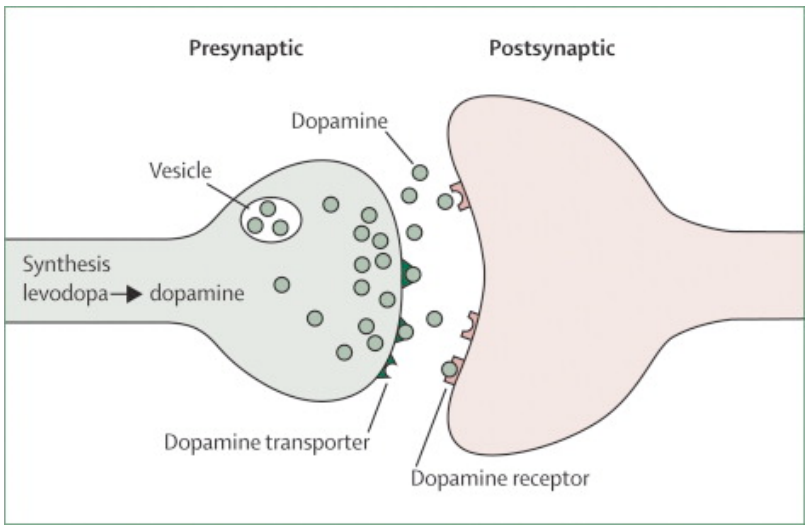

Fig. 1. Signal transmission at synapses, the site of action of the neurotransmitter

This means that the presynaptic segments of the connections between nerve cells produce a greater amount of dopamine during psychotic experiences (ca. 14% more), which is released into the synaptic cleft (Fusar-Poli et al., 2013a). This dopamine latches on to specific receptors at the post-synaptic area of the synapse, thereby transmitting the impulse to other nerve cells. A synapse can produce different neurotransmitters, and can "read" them at different specific receptor sites. In the case of psychotic experiences, dopaminergic hyperactivity takes place in a section of the basal ganglia (ventral corpus striatum) which is primarily involved in complex integrative processes such as curiosity, interpreting new events, motivation, attention, initiation of activity, rewards, reaction to aversive stimuli, emotions and the assignment of meaning or divergent interpretations ("aberrant salience"). At the same time, each brain region is connected with other areas through numerous nerve tracts and other neurotransmitters that can act in inhibiting or excitatory ways (networks), and also serve a regulatory function. In the case of psychoses, the prefrontal cortex seems to have a particularly important role due to lower dopaminergic activity and altered regulation of the glutamate system (another transmitter) (Laruelle, 2014; Slifstein et al., 2015).

At this juncture, a point of clarification is in order: we use the traditional term "schizophrenia" so that we can cite scientific studies. Schizophrenia is a construct possessing a great variety of divergent forms, expressions, trajectories and environmental sensitivities. Establishing it as a diagnosis is only moderately reliable, i.e. misdiagnoses are frequent, while the definition of this construct has been repeatedly changed over the past 100 years; most recently, in the DSM-V. The overlap among these various versions is less than 30%. From a basic science perspective, this construct has been increasingly questioned, either to emphasize the heterogeneity of the syndromes that it encompasses, or the soft boundaries of psychotic experiences reaching into the general population. Therefore, we generally put this term in quotation marks to remind the reader that it reflects a construct, rather than a factual entity.

Due to these complex interrelations, the elevation of subcortical dopaminergic activity in the striatum is not considered to be a *cause* of psychoses, but rather a correlate or final common pathophysiologic pathway (Howes & Kapur, 2009) resulting from a multitude of genetic, biological and social (i.e. primarily emotional) factors that have had their impacts earlier. In each individual case, there are always varying factors that act cumulatively and interactively (e.g. through epigenetically-caused expression of genes) on the person, his/her psyche, his body (e.g. through the hypophyseal-hypothalamic axis) and his/her brain as a "social organ" (e.g. via the pre-frontal cortex, superior temporal cortex, anterior cingular cortex, insula, meso-limbic dopamine system, amygdala and hippocampus (Meyer-Lindenberg & Tost, 2012). Furthermore, an insufficient availability of compensatory and protective experiences (relationships, classical social networks, etc.) plays a major role here.

Risk factors that have been studied up to this point are, for example (van Os et al., 2010; Varese et al., 2012; Read et al., 2013; Aderhold et al., 2009):

- biological and psychological complications during pregnancy
- stress during pregnancy
- unwanted pregnancy

- perinatal complications
- early loss of parental figures via death or abandonment
- unstable surroundings in early life
- separation of parents
- witnessing interparental violence
- dysfunctional parenting (often intergenerational)
- sexual, physical and emotional traumas
- neglect
- growing up in an urban environment
- social deprivations
- social rejection and defeat
- bullying
- racial or other forms of discrimination
- migration
- poverty

The first meta-analysis of studies of childhood adversities and trauma (Varese et al., 2012) finds that they substantially increase the risk of psychosis, with an OR of 2.8:

> Furthermore, the findings suggest that if the childhood adversities we examined as risk factors were entirely removed from the population (with the assumption that the pattern of the other risk factors remained unchanged), and assuming causality, the number of people with psychosis would be reduced by 33%. (Varese et al., 2012, p. 6/7)

Assuming causality here is justified, since in 9 out of 10 of the studies that tested for dose-response relations, these associations were positive (Varese et al., 2012).

As long as the person experiences psychotic symptoms, there is an elevated pre-synaptic release of dopamine. In an episodic course of a psychotic disorder this excessive discharge tends to subside ("phasic sensitization"), which is accompanied by a remission of the acute psychotic state. The precise mechanism that leads to the abatement of

excessive dopamine release, and thereby to a “spontaneous” remission of psychotic symptoms (natural remission or self-limitation of psychotic episodes), is just as mysterious as its origins. Presumably, there are individuals who experience psychotic symptoms without any significant changes in the dopaminergic system.

2. Effects of neuroleptics on dopamine receptors

We use the old term “neuroleptics,” because the notion of “antipsychotics” evokes an unjustified analogy of healing potential similar to antibiotics.

Oddly enough, neuroleptics do not directly impact the changes in the brain associated with psychotic experiences that were discussed earlier. This is due to the fact that they are not capable of normalizing excessive dopamine production or its release. Therefore, they cannot actually be considered curative. In fact, according to the latest scientific research, all neuroleptics act similarly by blocking (i.e. antagonizing) the post-synaptic dopamine-receptor subtype D2. This indirect mechanism of action is the cause of the functional and structural brain changes described later in chapters 3 and 4.

Neuroleptics engage for brief moments (“hit and run,” as in the case of clozapine or quetiapine) or for longer binding periods (several hours, as with haloperidol and risperidone) at post-synaptic receptor sites. Long-held hypotheses about particular advantages of second-generation neuroleptics due to additional serotonergic effects have been debunked by now. D2-blockade is therefore considered a necessary *and* sufficient mechanism of action for the antipsychotic effects of neuroleptics (Guillin et al., 2007).

2.1 Therapeutic window and dosage

Newer imaging techniques have revealed that a therapeutically meaningful blockade of D2 receptors by neuroleptics seems to occur within a "therapeutic window" when 50-70% of these receptors are blocked. This window is quite variable between different substances. Amisulpride, clozapine und quetiapine require a blockade of approximately

50-60% of receptors (Abi-Dargham et al., 2005), while haloperidol requires a blockade of 65%. A blockade above the upper limit does not result in additional reductions in symptoms, while side effects increase considerably. Some side effects are only noticeable above certain levels of blockade:

- prolactin elevations begin at 72% blockade (Kapur et al., 2000)
- extrapyramidal motor disturbances and akathisia > 78% (Kapur et al., 2000).
- clinically significant dysphoric reactions (listless, dejected) > 70% (Mizrahi et al., 2007)
- cognitive impairments > 70% (Mizrahi et al., 2007)
- aggravation of depressive and "negative" symptoms, so-called neuroleptic-induced negative symptoms, also known as neuroleptic-induced-deficit-syndrome > 70% (NIDS) (de Haan et al., 2000, Voruganti et al., 2001)

This applies equally to typical and atypical neuroleptics (de Haan et al., 2003). These side effects could be almost totally avoided by staying within the therapeutic window, and when they do occur, this is likely due to an excessive dose. Individuals with only minimally elevated dopamine release bear a particularly high risk for affective side effects (Voruganti et al., 2001).

The following additional side effects are also dose-dependent, without a specified therapeutic window:

- sudden cardiac death (Ray et al., 2001, 2009)
- myocardial infarction (Lin et al., 2014)
- metabolic side effects (Citrome, 2004; Correll et al., 2007)
- cardiovascular and cerebrovascular mortality (Osborn et al., 2007)
- sexual side effects (Besnard et al., 2014)

The individual acute dose necessary to reach this therapeutic window varies from patient to patient, but is generally quite low. An early study to identify appropriate dosage levels

(McEvoy et al., 1991) revisited the clinical concept of a "neuroleptic threshold." This principle was introduced 50 years ago by Haase in Germany, but to date has only been investigated in two small studies.

Those two isolated studies apparently exhaust scientific psychiatry's interest in this question, even though a great majority of patients appear to suffer in response to the usual clinical dosage levels. The McEvoy study revealed in 1991 that the optimal dosage range for most patients who had been previously exposed to a neuroleptic was between 4.3 ± 2.4 mg, i.e. between 1.9 and 6.5 mg haloperidol-equivalents (H-eq) per day, and that for 46% of the 106 patients in the study, the optimal dosage was even lower (around 2 mg or less). For individuals experiencing a first episode, the optimal dosage was at 2.1 ± 1.1 mg, i.e. between 1 and 3.2 mg H-Eq (McEvoy et al 1991), or less than half the dosage for patients who had previously been treated.

Consequently, dosage increases that occur in the course of treatment are mostly a result of changes at the receptor sites induced by those very same neuroleptics, as will be discussed further in chapter 4.

The following table can assist with the conversion of various drug dosages into haloperidol equivalents, and vice versa, especially when those are the only reference points given:

Generic Name	Brand	1 mg haloperidol corresponds to
NL 2nd Generation		
Aripiprazole	Abilify	3.4 mg
Clozapine	Clozaril	57.8 mg
Olanzapine	Zyprexa	2.5 mg
Quetiapine	Seroquel	76 mg
Risperidone	Risperdal	0.7 mg
NL 1st Generation		
Chlropromazine	Thorazine	54 mg
Fluphenazine	Prolixin	1 mg
Haloperidol	Haldol	1 mg
Perphenazine	Trilafon	3.7 mg
Thioridazine	Mellaril	47 mg
Trifluoperazine	Stelazine	2.ymg
Depot Preparations		
Fluphenazine decanoate	Prolixin Decanoate	1.25 mg/2-3 weeks
Haloperidol decanoate	Haldol Decanoate	18.9 mg/4 weeks
Risperidone -Poly-DL-lactid-glycolid	Risperdal Consta	10 mg/2 weeks

Table 1. Haloperidol equivalents (from Andreasen et al., 2010.)

In spite of the fact that the McEvoy study mentioned above was carried out by a highly respected group of researchers, and that these dose ranges are quoted quite often, it had virtually no impact on clinical practice, with harmful consequences for patients. But this is not all. Over the next 15 years, comparison studies between so-called "typical" and "atypical" neuroleptics utilized dosages for "typicals" (mostly haloperidol, the drug with the greatest untoward effects) above 10 mg in 80% of the studies, and 20 mg and higher in 20% of them, in order to achieve more favorable results for the "atypicals"; in particular, fewer neurologic and sedative side effects (Hugenholtz et al., 2006). Many

respected scientists have participated in and benefited from these clearly misleading studies.

A subsequent review of all existing placebo-controlled studies concerning dose-effect relations of second-generation neuroleptics (Davis & Chen, 2004) found surprisingly low upper limits of effective dosages for most of the drugs in "typical multi-episode patients" diagnosed with "schizophrenia" who had already been treated with drugs. Hardly any further symptom-reducing effects could be found above dosages near that maximal level. Due to the sigmoidal curve of dose-effect relationships, the optimal dose of a neuroleptic lies at the upper end of an ascending but then rapidly flattening curve (ED^{95} = near-maximal effective dose range = 95%).

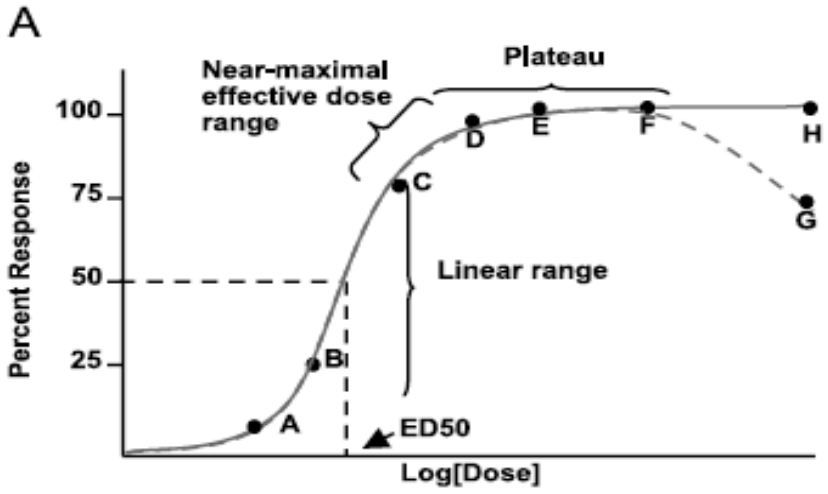

Fig. 2: A schematic dose-response curve of neuroleptics (from: Davis & Cheng, 2004, p. 193)

Such a dose suffices to achieve maximal clinical remission of symptoms, and any further increase has only minimal and clinically irrelevant effects on symptoms, while causing increasing side effects. Due to the fact that symptom reduction at a certain dosage can take 4 weeks or longer while remaining incomplete, in routine clinical situations the dosage is frequently increased too soon and too rapidly, when no additional symptom reduction can be discerned. This common dosing practice is known as "overshooting."

At this point, we would like to list the generally adequate dosages for certain neuroleptics when treating patients who have already experienced repeated episodes of psychosis, for which they were previously treated with such medications:

- For most patients, the ED^{95} of haloperidol is between 3.3 - 4 mg, and only a small minority would benefit from 10 mg per day. Accordingly, a rather broad dosage range of 3.3 – 10 mg is listed for haloperidol below. Dosages beyond this individual threshold are not more effective, according to 42 studies involving 1821 subjects (Davis & Chen, 2004). This is especially true for the group of patients who experience little reduction of symptoms at dosages up to 10 mg/day, often referred to as "treatment resistant." Raising the dosage above this level did not result in greater remission for such patients either. These varied studies report quite similar results concerning this issue. Consequently, available research does not support the existence of a particular group of patients who might benefit from higher dosages of neuroleptics. Individual cases may differ.

- A dosage of aripiprazole of 2 mg/day is nearly as effective as 10-30 mg/day.

- A daily dosage of 100 mg amisulpride was only marginally less effective than higher doses, suggesting an ED^{95} of 200 mg.

- Olanzapine presumably has an ED^{95} around 18-20 mg per day (one study).

- The largest effects of quetiapine occurred below 150 mg, which were quite close to the effects around 360 mg. Higher dosages of this substance had somewhat lesser positive effects, especially around 750 mg per day.

- Clozapine has shown better effects at higher serum levels in partial- or non-responders. That is why it is often given at dosages above 400 mg/day. Individual dosages can be much lower. Therefore, a gradual dose increase is quite important here. When there is no response at the usual dosages, monitoring of serum levels (at least 350-400 ng/ml) can be helpful in finding the right dose. (Citrome et al., 2002).

Table 2 (below) shows the ED^{95} values for various neuroleptics as calculated by Davis and Chang, contrasted with the guidelines for schizophrenia treatment prepared by the German Society for Psychiatry and Neurology (DGPPN), 2005.

Substance	DPPN, 2005 Dosage goal/day	Davis et al., 2004 Effective dose 95%/day
Amisulpride	400-800 mg	200 mg (100 mg. slightly less effective than higher doses)
Aripiprazole	15-30 mg	10 mg (2 mg. nearly as effective)
Clozapine	200-454 mg	> 400 mg
Olanzapine	5-20 mg	> 16 mg (also > 20 mg)
Quetiapine	400-750 mg	150-600 mg (i.e. a subgroup of patients can achieve maximum effectiveness at 150 mg)
Risperidone	3-6 mg (<10 mg)	4 mg
Risperidone Consta	No information	25 mg/14 days
Ziprasidone	80-160 mg	120-160 mg

A gradual approach with incremental increases is essential to find the optimal dosage for each individual patient, since the sufficient dose for any one person might actually be either below or above that amount. Dosage titration over several weeks has a better chance of resulting in the lowest possible dose, since nearly 80% of the full effect occurs with a delay of 4 weeks. Should a dosage increase not lead to greater symptom reduction within 4-6 weeks, it should be retracted, even if residual symptoms persist. Since there were no randomized studies of dose-finding strategies below 3 mg haloperidol equivalents considered in Davis & Chen's 2004 review, it can be assumed that individually adequate dosages are much more frequently lower than ED95 rather than

above the upper limit. This has also been demonstrated in a later randomized study by Wunderink et al. (2013) with lower dosages, which will be described in detail in chapter 7.1.

Wunderink and his collaborators recommend an individualized dosage-finding strategy for each patient by trial and error, and criticize guidelines based on fixed dosages. They conclude that treatment guidelines often contain erroneous dosage recommendations, resulting in excessive dosages during routine clinical practice.

The meta-analyses used in so-called evidence-based medicine, such as those from the Cochrane Collaboration, only deal with data from randomized studies which are considered particularly valuable. Complex questions that emerge from everyday practice cannot be investigated in this manner. Therefore, we need to conclude that the lower dosage limits given in such reviews are generally still too high. One Cochrane meta-analysis by Wairach et al. (2002) on the use of haloperidol in the acute treatment of "uncomplicated schizophrenia" reported a dosage of 3 - 7.5 mg per day. The upper limit was defined arbitrarily, without substantiation.

2.1.1 Cytochrome P 450 polymorphism

In addition, individual differences in the metabolism of neuroleptics have to be taken into consideration for establishing an effective dose for individual patients. For instance, 20% of the Caucasian population are slow or very slow metabolizers due to a specific peculiarity (polymorphism) of the liver-enzyme CYP450-2D6. Such "poor metabolizers" need a significantly lower dose than, for example, 2 to 4 mg of haloperidol or other neuroleptics that pass through the liver. Conversely, an ultra-rapid metabolization [metabolism] among 2-3% of the Caucasian population may be *one* reason for apparent "treatment-resistance." Such individuals end up requiring much higher dosages (Schwab et al., 2002). Therefore, an assessment of CYP450-2D6 makes sense for haloperidol, perphenazine, zuclopenthixol, thioridazine, risperidone, iloperidone and aripiprazol. Whenever a polymorphism for "poor metabolizers" has been demonstrated, a dose-

reduction by around 50% or a switch to another substance, is highly recommended, in order to forestall severe side effects (Ravyn et al., 2013; Swen et al., 2011).

2.2 Minimal dosing

To arrive at the lowest possible effective dosage, one needs to raise the dose from the lowest limit gradually, at intervals of several weeks, whenever there is no reduction of symptoms at any given dose. The ultimate target dose for each person cannot be predicted. Differences among individuals are large, i.e. 300% or more (de Haan et al., 2003; Davis et al., 2004). The results that can be expected depend as much on time as on the dosage. It often takes 12 to 24 weeks until a substantial remission under neuroleptic treatment can be achieved (Emsley et al., 2006). In some cases (15%), the maximal effects might only occur after 5 to 12 months (Robinson et al., 2005). Sometimes, only a partial remission occurs. The endpoint of such a partial remission is also uncertain, and can vary considerably from patient to patient. All too often, dosages are raised prematurely or a combination of drugs initiated, resulting in excessive dosages ("over-shooting") with greater side effects.

The lowest but still quite effective dosage for individuals experiencing a first episode of "schizophrenia, schizophreniform or schizoaffective" psychosis has been determined in a clinical study of 35 patients who were given an initial dose of 1 mg haloperidol (Oosthuizen et al., 2001). This dose was maintained over 4 weeks (one patient's dose was even lowered to 0.5 mg due to side effects). The dose was increased to 2 mg only when the effects were inadequate. If the "positive" symptomatology (defined primarily as hallucinations, delusions, thought disorders) had not abated sufficiently after an additional 3 weeks, a weekly augmentation of 1 mg/day ensued. Following this procedure, 55% of the patients could be treated with just 1 mg daily, while only 20% required an increase to 3 or 4 mg. No dose higher than 4 mg was given in this study. Overall remission of symptoms was quite good. According to the response criteria of Lieberman et al. (2000), the percentage of responders after 3 months was 65.7% and the mean PANSS-positive value (Positive and Negative Symptom Scale) fell from 25 to 10 points (range 7-42). Treatment had to be stopped in only 8.5% of study-participants

(3/35). Since this study was not randomized, it has not been referenced in any treatment guidelines.

Using the lowest possible dose averts or reduces the incidence of many side effects and leads to a very low prophylactic maintenance dose. On the other hand, an initial "dysphoric" reaction, mostly a reaction to excessive dosages, is one of the best predictors of subsequent medication "non-compliance" (van Putten et al., 1974, 1981; Hoggan et al., 1983). There may indeed be an inverse relationship between rapid symptom reduction and ongoing medication adherence. No neurobiological finding supports the current practice of forced symptom suppression with neuroleptics, especially when considering that ongoing adherence might be of much greater importance.

The required dose levels of neuroleptics depend greatly on the quality of the psychosocial and psychotherapeutic treatment (for example "Need-Adapted Treatment," see chapter 8.3) or therapeutic milieu during acute interventions (for example, in a Soteria residence or an inpatient unit with Soteria elements). Soteria consists of a therapeutic milieu for 7 to 8 individuals who are experiencing acute psychoses in a small residential setting where they are given intensive individual support ("being with"). A comparative study of Soteria Berne (Switzerland) was able to show that neuroleptic dosages could be reduced to one-third of the usual in a protective, low-stimulus environment housing 8 patients (Ciompi et al., 1993).

Neuroleptics—if they are effective at all—merely bring about a distancing and mitigation of delusional experiences, but generally no actual correction of their content (Kapur et al., 2006). This is also demonstrated by the fact that relapses often involve similar delusional beliefs. For the most part, only after a course of individual psychotherapy and new learning experiences do survivors manage to effect an actual transformation of their "delusional" beliefs, and to integrate these experiences into a meaningful context including their biography. Psychotic experiences often express specific biographical material in encrypted form that thus far could not be discussed openly, especially concerning the family and other important individuals. More often than not, this material

relates to traumatic experiences. Fifty percent of individuals diagnosed with "schizophrenia" report traumatic life experiences (Morgan & Fisher, 2007). From this perspective, psychoses can also be understood as ineffective attempts to solve deep-rooted problems. To think of them merely as symptoms of a disorder and call for their suppression is an erroneous oversimplification. Neuroleptics cannot replace psychosocial and psychotherapeutic interventions; they can only support them, if they are needed at all.

2.3 Excessive dosages and polypharmacy

In spite of the fact that dose augmentations do not appear to make sense, many patients in routine clinical settings are being treated with excessive dosages and/or a combination of several neuroleptics in response to a persistence of symptoms. The American Psychiatric Association (APA) addressed the issue of polypharmacy in their 2014 special appeal, "Choosing Wisely:"

> Do not routinely prescribe two or more neuroleptics simultaneously. The research shows that 2 or more neuroleptics are prescribed in 4-35% of ambulatory and 30-50% of hospitalized patients. This occurs in spite of the fact that the effectiveness and safety of combining several neuroleptics has not been demonstrated, and the risk of interactions with other drugs, non-compliance and medication errors seems elevated. The use of two or more neuroleptics should generally be avoided, except in cases where three attempts at monotherapy have failed, including at least one trial with clozapine, whenever possible, or an attempt to introduce a second antipsychotic, if the second one has been introduced with the intention of switching from one to another drug [e.g., a cross-titration in pursuit of monotherapy].

A multi-center study in 10 German hospitals has determined that, between 2003 and 2006, 44% of patients with two inpatient stays longer than thirty days were treated with polypharmacy (Schmidt-Kraepelin et al., 2013). This occurs in spite of the fact that there is no scientific proof for the efficacy of two or more neuroleptics in combination. Most

patients are not informed about the lack of a scientific basis for these combinations. In the rare instances when an improvement under polypharmacy is noted, it is usually rather small, i.e. around an 18% reduction of BPRS or PANSS ratings (Taylor et al., 2009). Such improvements always need to be considered in conjunction with the additional risk of side effects. Early use of combinations is particularly nonsensical. The greater the difference in the types of receptors being blocked by different neuroleptics ("receptor-binding profile"), the more side effects can be expected. Thus, the risk of weight gain, diabetes (Essock et al., 2011; Citrome et al., 2004), disturbed movements, QT-interval prolongations with an increased risk of sudden cardiac death, sexual dysfunction, and aggravation of positive symptoms is increased (Messer et al., 2006). On top of this, cognitive deterioration can occur (Hori et al., 2006, 2013; Élie et al., 2010; Chakos et al., 2006) as well as additional atrophy of grey and white brain-matter, especially in the frontal lobes, that corresponds to higher total doses.

Only monotherapy with Clozaril (and much less so, with amisulpride and olanzapine), rather than any kind of combination of neuroleptics, seems to have a somewhat better effect than other antipsychotics. In the rare situation when there is no sufficient effect from clozapine alone, there might be some justification in spite of the limited evidence to add sulpride or amisulpride. A daily dose of 600 mg amisulpride might make sense in such situations (Assion et al., 2008). Actual symptom reduction under such a combination is however rather weak, at 18%. A combination of clozapine and aripiprazole has been noted to result in weight reduction according to some studies, with a mean reduction of 2.7 kg within 6 weeks (Henderson et al., 2006) and 5 kg within 34 weeks when the average baseline weight was 90 kg under clozapine (Karunakaran et al., 2007).

Any additional effects of certain combinations frequently do not become apparent for a number of weeks, quite possibly even for as long as 3 months. Additional side effects such as weight gain, metabolic changes, etc. should be taken into consideration. In particular, metabolic changes and cardiac conduction (EKG) should be assessed prior to the initiation, and again after 4 or 12 weeks of combined treatment. Ideally, cognitive

functioning should also be assessed before and throughout treatment with such combinations. If there are further side effects, the patient must be given a choice between continuation of this treatment or a return to monotherapy. Patients should be aided in this decision by close members of their support network, and they should be made aware of the potential impact of these side effects. Should the drug combination show no notable effects within 3 months, it should be discontinued.

2.4 Dose reduction and return to monotherapy

Some studies show that a gradual reduction of an excessive dose generally does not lead to an increase in relapses, and might actually be associated with a reduction of persistent positive symptoms (Liberma et al., 1994; Lerner et al., 1995; van Putten et al., 1993). Reducing polypharmacy from an average of 3.6 neuroleptics and a total dose greater than 1000 mg CPZ-equivalents was successful in 88% of the patients, leading to an average of 59% dose reduction. Fifty-six percent of the patients showed clinical improvements, while 32% remained unchanged. Brief deteriorations in 12% of the subjects were reversed by returning to prior dosage levels (Suzuki et al., 2003, 2004).

In 69% of the cases, the switch from two neuroleptics to only one was also successful. Monotherapy was accompanied by a weight reduction of about 5 lbs. over six months, while polypharmacy resulted in weight gain (Essock et al., 2011). Another study showed an enhancement of attention and executive functions, as well as improved daily functioning and occupational capabilities, when the patient gradually changed from two neuroleptics to a single neuroleptic (Hori et al., 2013).

Sudden discontinuation of antipsychotics is contraindicated, especially due to a three-fold risk of relapse (Gilbert et al., 1995; Viguera et al., 1997; Baldessarini et al., 1995). However, such an increase in relapse rates did not appear in the meta-analysis conducted by Leucht et al. (2012). Two-thirds of these studies involved abrupt withdrawal, while one-third used a tapered discontinuation with an average length of four weeks, usually by stopping a depot preparation (Leucht et al., 2012, p. 2067). A gradual reduction of the

dose by 10% every 4-6 weeks, along with careful monitoring of mental changes, seems to yield the best results. This is discussed further in chapter 7.

The fact that current clinical practice seems rather untouched by these discoveries might have something to do with lack of information. Presumably, economic pressures mandating short inpatient stays play an important role; the adverse results of such treatments are generally not witnessed by hospital staff, since they appear only later. Psychiatrists working in outpatient settings see their patients only briefly and infrequently, and are often struggling to undo a combination regimen that had been introduced during an earlier hospitalization. Furthermore, suitable outpatient psychotherapy is only rarely available. Relatives and other supporters are also not included in the decision-making process, even though they might be most familiar with the patient and his/her situation.

3. Effectiveness of neuroleptics for disorders within the "schizophrenia" spectrum

3.1 Variable patient trajectories on antipsychotics

Levine et al. (2010) have analyzed the data from a randomized study of 491 early interventions (less than three months prior treatment) of individuals diagnosed with "schizophrenia, schizophreniform or schizoaffective" disorders, and identified the following five trajectories (i.e. course of "illness") that occurred in conjunction with the first six months of treatment with neuroleptics (risperidone or haloperidol). The severity of symptoms in these studies was assessed with the PANSS (Positive and Negative Symptom Scale).

Trajectory	Percentage of sample	Assessment	Decrease in PANSS after 6 weeks	Drop-Outs
1	14.9%	Mild symptoms at onset	59%	29.7%
2	22.3%	Mild symptoms at onset	29%	46.8%
3	31.3%	Minimal improvement	19%	65.8%
4	17.1%	Considerable symptoms at onset, greatest improvement	76%	37.6%
5	14.5%	Considerable symptoms at onset, modest improvement	20%	65.3%

Table 3: Trajectories of neuroleptic effects during initial treatment (from Levine et al, 2010).

The figure below shows the five trajectories over time.

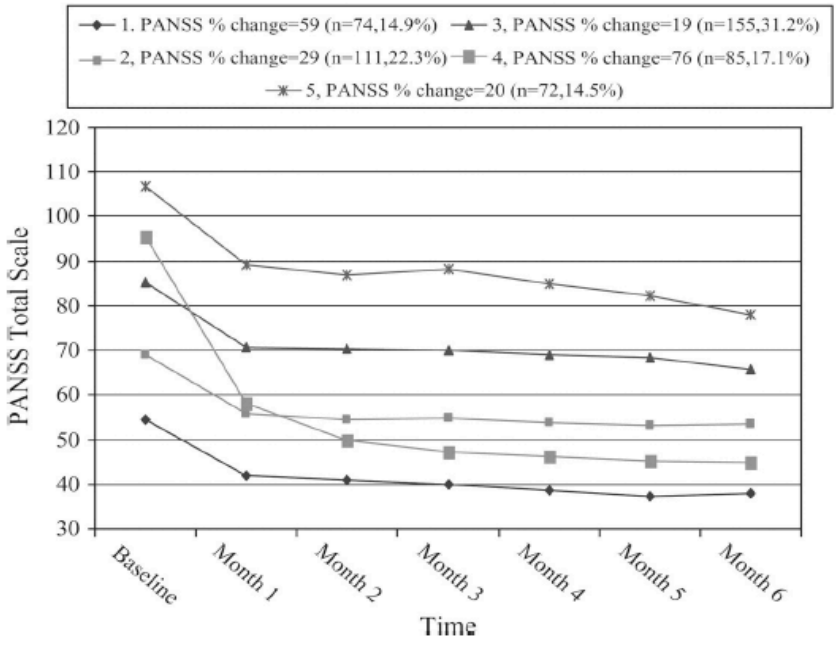

Figure 3: Course trajectories with treatment over six months (from: Levine et al., 2010, p. 62)

Sixty-eight percent of the subjects (trajectories 2, 3 and 5) showed less than 30% improvement in their PANSS ratings, even if the initial symptoms had been mild. The dropout rate in these sub-groups was very high. Only 32% of the sample (trajectories 1 & 4) showed a reduction in their PANSS ratings, of 59% and 76%, respectively, after six months. But even these good-responder groups had dropout rates of 30% and 37%. To assess the long-term effectiveness of neuroleptics, we must consider the fact that in this

study involving treatment of first-episode patients, no group experienced deterioration of symptoms while being treated with neuroleptics (no increase for the curves in diagram Fig. 3). This is an important finding when contrasted with the long-term treatment described later (see Fig. 4), in which patients who had experienced earlier episodes and were treated with neuroleptics over a longer period showed a much less positive response to the drugs.

In a placebo-controlled study conducted in collaboration with Eli Lilly Inc., patients previously treated with neuroleptics (length of period not specified/assessed) were exposed to olanzapine or haloperidol for six weeks. The following results were obtained (as usual, the placebo-group had been recruited from patients for whom neuroleptics had been discontinued within 4-7 days after initiation) (Marques et al., 2010):

Trajectory	Percentage of sample	Assessment	Decrease in PANSS after 6 weeks
1	10%	Dramatic responder	74%
2	22%	Responders	50% = placebo
3	48%	Partial responders	20% = placebo
4	20%	Non-responders	No reduction

Table 4. Trajectories of neuroleptic effects in pretreated patients (from Marques et al, 2010)

Only the first small group (10% of total sample) showed a rapid and marked reduction of symptoms due to neuroleptic treatment. A second group (22% of sample) showed a substantial 50% reduction of symptoms, and a third group (48% of sample) experienced a 20% reduction, which is barely clinically notable. Twenty percent of subjects showed no effects at all (aka non-responders). The reduction of symptoms in the second and third groups (together nearly 70% of the total sample) did not show significant ("robust") differences from the placebo group.

Even regarding maintenance treatment with the "second generation antipsychotics" (SGAs) olanzapine, risperidone, quetiapine and ziprasidone, and the "first generation

antipsychotic“ (FGA) perphenazine, an analysis of data from the CATIE study arrives at rather sobering results (Levine et al., 2012). In this study, subjects who had previously been exposed to antipsychotics and who were assessed as moderate to severely ill were randomly assigned to olanzapine, perphenazine, quetiapine, risperidone and ziprasidone for treatment over 18 months if possible. For most of them, this was not an acute treatment episode but a change from one antipsychotic to another. An increase in PANSS scores represents deterioration. The following illustration shows the results only for the 27% of subjects who completed the study. Four trajectories were revealed over the course of the 18 months.

Trajectory	Percentage of sample	Assessment	Decrease or increase in PANSS after 18 months
1	31.5%	Responders	Decrease by 28%
2	8.4%	Initial responders, then deterioration	Decrease/increase by 20%
3	36.4%	Consistent gradual deterioration	increase by 5-10%
4	23.7%	Consistent significant deterioration	Increase by 30%

Table 5: Trajectories of neuroleptics effects in long-term treatment for study completers (Levine, et al., 2012)

This 18-month course can also be depicted over time. The figure below is a graphic display of the four trajectories. An upward slope for the curve indicates symptomatic deterioration.

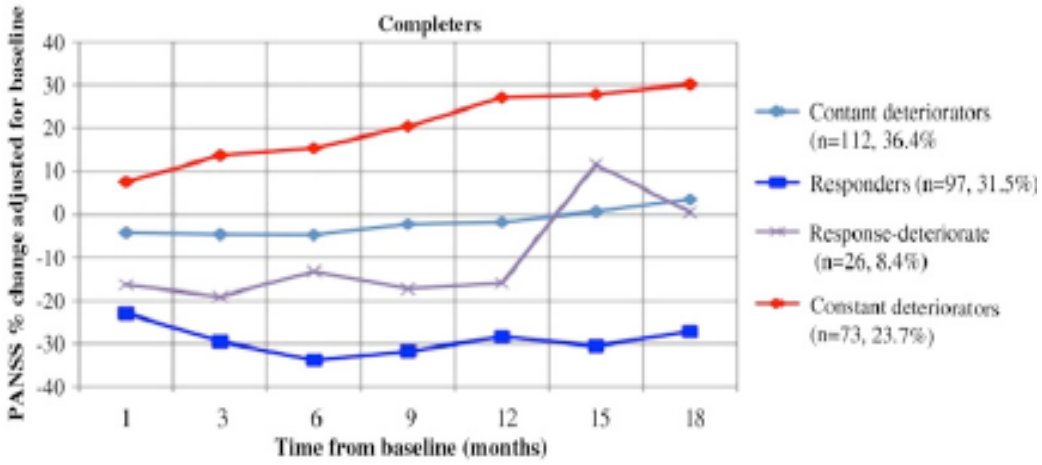

Figure 4. Course of trajectories for study completers with long-term treatment. CATIE study. (From Levine et. al, 2012, p. 143.)

Within the trajectory "responders," the following results were achieved for each neuroleptic within 18 months of follow up:

- Patients treated with olanzapine showed an initial improvement of 32.5% reduction in PANSS scores, which gradually decreased over time to a total reduction of 5%.

- Those taking perphenazine experienced a 21.7% initial improvement, which similarly yielded only a 2% improvement over 18 months.

- Risperidone, quetiapine and ziprasidone showed maximal improvement rates of less than 15% reduction in PANSS scores at all times.

The only clinically significant - albeit temporary - improvement occurred under olanzapine, and to a lesser extent, under perphenazine.

Primarily, this study shows that long-term treatment with neuroleptics leads to a worsening of symptoms over time for a large group of patients. This deterioration occurred in 60% of CATIE subjects from the beginning, as well as in the other 40%

following an initial improvement during the first six months.

Similarly to Levine's study (2010) of first episodes, where subjects who dropped out experienced a significantly lower response rate, this study reveals an even greater rate of deterioration among the 68% of subjects who failed to complete the study. The dropout rates, in themselves, constitute a particularly negative result. Consequently, unilateral discontinuation or non-adherence to medications has to be reconsidered. It should not be seen as the cause, but rather as a result of the unfavorable long-term course of neuroleptic treatment. The fact that such discontinuations occur abruptly and without professional support contributes to their frequent failure. The following figure shows all PANSS-ratings for as long as patients remained available for follow-up.

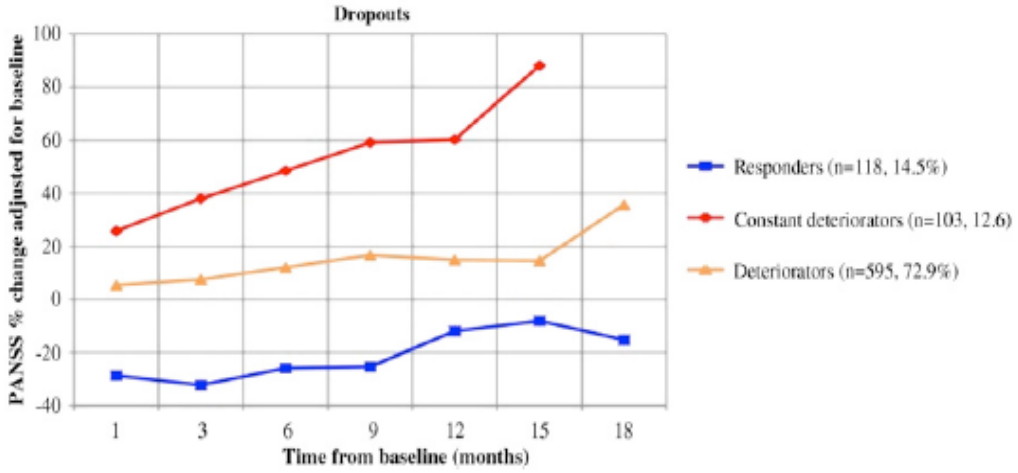

Fig. 5: Course of trajectories for dropouts from long-term treatment, CATIE study (from: Levine et al 2012, p. 143)

Correspondingly, a review of 120 studies, including a total of 9500 patients with previous neuroleptic treatment, showed only "less than minimal effects" on psychotic symptoms in comparison to placebo (Lepping et al., 2011). Whenever the Brief Psychiatric Rating Scale (BPRS) was used to assess outcomes, most neuroleptics of the first and second generation yielded minimal clinical improvements, while according to the PANSS—an instrument more specific to psychosis—even fewer medications provided even this minimal benefit. Amisulpride and olanzapine appeared to be the most effective agents.

In a meta-analysis of 38 studies with a total of 7323 subjects—most of them sponsored by the pharmaceutical industry—only 17% of participants showed greater effects than placebo (NNT=6) (Leucht et al., 2009). (NNT, "number needed to treat" is a statistical variable that indicates how many patients per unit of time, i.e. 1 year, need to be treated with a particular substance or intervention in order to achieve the desired treatment goal for one patient.)

In the so-called placebo groups in these studies, 86% of the studies reported that neuroleptics were withdrawn from this group in less than six days. As such, these "placebo" groups should instead be considered "discontinuation" where patients are more likely to experience additional psychotic withdrawal symptoms (see below following page 89). Such discontinuations interfere with the potential for spontaneous remissions, and exaggerate any differences in the effectiveness of neuroleptics that would favor the experimental group. However, this issue is not mentioned in Leucht's meta-analysis. Even so, the overall effects of neuroleptics were clinically insignificant: "We pooled the more recent studies that use the PANSS and found a difference of 10 points. According to Leucht et al. (2006a) a PANSS total score difference of 15 points reflects minimal improvement according to the CGI." (Leucht et al., 2009).

Dropout rates in these studies were generally higher than 50%, suggesting that the studies were basically methodologically inadequate. These results were also confirmed by an analysis of studies submitted to the U.S. Food and Drug Administration (FDA) in support of an approval for specific drugs (Khin et al., 2012). The FDA data show an increase in placebo effects and decrease in treatment effects since 1999 (PANSS reduction by 6 points, compared to 10.8 points in earlier studies). Treatment effects also diminished when body weight increased. Most studies followed subjects for 16 weeks or less. Dropout rates were generally around 50%. The most common reason for dropout was lack of efficacy. Thus, there are essentially no methodologically adequate long-term studies of neuroleptic treatment (Leucht et al., 2008).

The data for patients experiencing a first episode of "schizophrenia-spectrum" disorder are surprisingly so limited that the effectiveness of neuroleptics cannot be convincingly assessed for such individuals (Bola et al., Cochrane 2011). When including quasi-experimental studies with a suitable comparison group but without randomization, it appears that 40% of such patients can be treated entirely without neuroleptics, evidencing further mild-to-moderate advantages over a period of two years. Experimental success for such an approach has been demonstrated in the case of the Soteria and Need-Adapted-Treatment models.

Also, newer approaches to recovery show the potential for the reduction and discontinuation of antipsychotic drugs, but without evidence from clinical studies (as outlined, for example, in Amering & Schmolke 2012).

Recovery rates in naturalistic outcome studies since the introduction of neuroleptics do not show improvements, but instead an overall tendency towards deterioration (p=. 704).

Period	Number of Studies	Median	Interquartile range*
1941-1955	5	17.7%	13.0-19.7 (%)
1956-1975	11	16.9%	16.3-32.4 (%)
1976-1995	19	9.9%	5.8-19.0 (%)
After 1996	2	6.0%	3.9-8.1%

Table 6. Recovery rates in studies from 1941 to present ((Jääskeläinen et al 2013, p. 8, Table 1). *The interquartile range (IQR), also called the midspread or middle fifty, is a measure of statistical dispersion.

In their systematic meta-analysis of recovery rates for "schizophrenia" Jääskeläinen et al. (2013) made the following comment: "This is a sobering finding—despite major changes in the delivery of care to people with schizophrenia (e.g., deinstitutionalization, antipsychotic medications, psychosocial interventions, and early psychosis services), the proportion of those who met recovery criteria have not improved over time. However, the

studies in this meta-analysis are naturalistic, and we do not know what kind of treatment the patients received. Thus, conclusions about the effect of treatments are not possible." (p. 304)

How can we explain these limited, but widely overestimated, results of neuroleptic treatment?

3.2 Differences between first- and second-generation neuroleptics

For more than a decade, proving a difference between these two groups of substances has been emerging as a central issue in the treatment of individuals with psychoses. The overestimation of second-generation neuroleptics resulted primarily from distorted study designs, selective publication of results, and unpublished studies (Spielmans et al., 2010) and was only corrected due to studies that were independent of the pharmaceutical industry. Psychiatry emerged rather bruised from this historical period, having become a dependent, deceiving and deceived "paradise of the pharmaceutical industry" (Götzsche, 2013). Societal attempts to repair this dependent relationship, which frequently bordered on corruption, continue to this day.

Today, almost no one remains convinced of a clinically significant advantage in effectiveness of so-called "atypical" neuroleptics in comparison to the older "typicals" (Meltzer, 2013). (A glossary of atypical and depot neuroleptics is appended to this text.) Overall, clozapine is considered the most effective substance. Some psychiatrists are already calling for the abolishment of the distinction between typical and atypical neuroleptics (Kendall, 2011; Kane et al., 2010) due to the fact that no fundamental difference seems to exist between these two groups. A former vice president of Eli Lilly wrote that "not one drug with an entirely new mechanism of action has reached the psychiatric market in the past thirty years" (Fibiger, 2012). Therefore, it has become acceptable to speak of first- and second-generation antipsychotics (FGA & SGA), as opposed to antipsychotics and atypical antipsychotics.

In 2013, Leucht et al. published a meta-analysis of randomized studies that investigated

the differences between various SGAs and FGAs. Clozapine, amisulpride, olanzapine and risperidone were found to be significantly more effective, in descending order, over six weeks. On page 8 of their publication, the reader will find the following comment: "However, for perspective, the efficacy differences compared with placebo were of only medium size (0·33–0·88, median 0·44), so the differences in efficacy between drugs are possibly substantial enough to be clinically important" (p. 959). Their meta-analysis did not shed light on this question. It is surprising/astonishing that the authors find it justified to formulate this assumption. Since in two previous meta-analyzes of RCT on the efficacy of SGA, - as already mentioned - not even the difference between the treatment groups and placebo groups (i.e. neuroleptic withdrawl) with similar effect sizes reached a level of minimal improvement according to the CGI (Leucht et al., 2009, p. 440) with amisulpride only as a more effective exception (Lepping et al 2011).
Based on these results, Leucht et al. question whether there is a useful distinction to be made between FGA and SGAs.

User-survivors have pointed out that in spite of general research results, individual effects of neuroleptics can vary greatly, suggesting that certain substances can be considerably more effective than might be expected based on the research. In cases where there are not substantial side effects at the onset of treatment, a change of medication should only be contemplated after 3 months. Within this period, the achievable effects can be adequately assessed. One should also keep in mind that side effects can be quite variable among different individuals, even if the neuroleptic taken belongs to the same class of substances. Minor side effects can be significant enough for certain individuals as to offset any greater benefits they might ultimately experience with this substance.

3.3. Long-term course of schizophrenia with and without neuroleptics

A long-term follow-up study by Harrow et al. (2014) is relevant for an assessment of long-term course and outcome with or without neuroleptics, and the potential for successful discontinuation under naturalistic conditions. Since there are no placebo-controlled studies over a period longer than 3 years (Leucht et al., 2012), this study is even more significant. Seventy participants, mostly in the midst of their first episode of psychosis with diagnoses in the schizophrenia spectrum (DSM-III) (61 with a

schizophrenia and 9 with a schizoaffective diagnosis), were followed over a period of 15 (N=64) or 20 years (N=59) with 5 or 6 points of assessment. Initially, all participants had been experiencing symptoms for over 6 months. "At index hospitalization, the patients were consecutive admissions within the limitation of giving preference to younger (between 17- and 32-year-old at index) patients with fewer previous hospitalizations" (Harrow, 2007, p. 407), and all were admitted consecutively to 2 hospitals (46% for the first time, 21% for the second time, 23% more often). All received neuroleptics at the beginning, but 70% discontinued them against medical advice within the first 2 years. After 2 years, 33% were off neuroleptics, and after 20 years, 38% were off them, with a small gradual increase at every follow-up.

When percentages of patients in recovery within the groups on and off antipsychotics at each follow up were compared, a significantly larger percentage of SZ not on antipsychotics for prolonged periods experienced periods of recovery which also requires adequate work and social functioning and did not relapse more frequently. This effect started at the 4.5-year follow-up and continued thereafter over the next 15 years. Forty percent of the entire sample had at least one follow-up exam where they were in full recovery, suggesting a basic potential for recovery under favorable conditions.

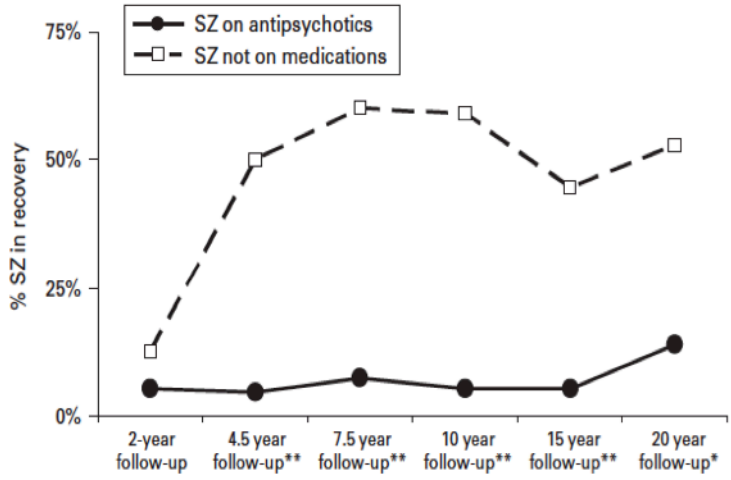

Fig. 6. Relationship between recovery and use of antipsychotics in schizophrenia at each time point over 20 years (from: Harrow et al., 2012, p. 4)

A more detailed subgroup analysis provides further interesting information: Of the total group, 34% of the patients were prescribed antipsychotic medications at every one of the follow-up assessments (Group 1), and 45% were prescribed antipsychotic medications at some, but not all, of the follow ups (Group 2). The remaining 21% were not on antipsychotics at any of the follow-up assessments (beginning at 2 years) over the 20-year period (Group 3). Within Group 1, i.e. those with ongoing neuroleptic prescriptions, 44% exhibited continuous psychotic symptoms, 72% exhibited such symptoms at 4 out of 5 (or 6) follow-ups, and 28% had the symptoms only at two time points and showed at least one period without psychotic experiences. Twenty percent of the total sample showed no psychotic symptoms at any follow-up point; however, none of these were in Group 1.

Figure 7 (below) shows a comparison of psychotic symptoms between Groups 1 and 3. After two years, there was no significant difference between these groups as far as symptoms are concerned. With further passage of time, however, this difference became increasingly large and ultimately significant, favoring Group 3—the off-antipsychotics group—up until the 15th year ($p<0.001$). By year 20, this difference has lessened, but is still significant ($p<0.01$). 12 of the 15 subjects who had discontinued neuroleptics completely before year 2 still had symptoms at year two, but 57% of this group were free of symptoms after 4.5 years, and therefore remitted without neuroleptics.

Conversely more than half of Group 1 – always on neuroleptics - had one or more periods without psychotic symptoms. However, under maintenance medication, psychotic symptoms seemed to recur. After 2-3 years, the effectiveness of antipsychotics seemed to be waning, or might even have begun to have a reverse effect. For instance, those phases within the long-term trajectory when people experienced significant symptomatic and functional improvement seemed more pronounced when they were not taking neuroleptics.

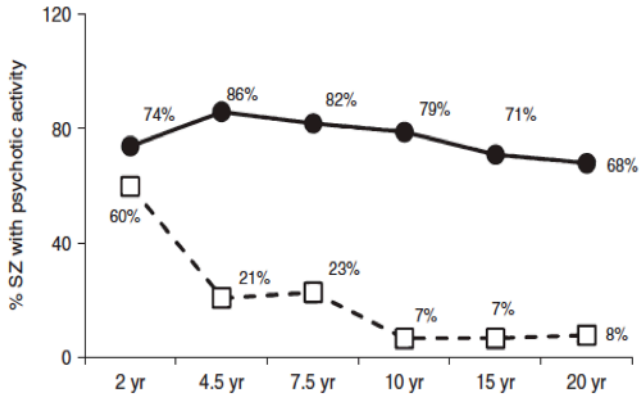

Fig. 7: Psychotic activity over 20 years with and without neuroleptics. The black circles are for those always prescribed antipsychotics; the white squares are for those not prescribed psychiatric medications at any assessment (from Harrow et al., 2014, p. 4)

Although this self-selected group off medication at follow ups had better premorbid developmental achievements and more favorable prognostic factors (Harrow et al 2007), it is rather unlikely that the group of patients who did not take neuroleptics continuously just represents a selection of people with a better prognosis, since patients with a poorer prognosis also experienced fewer symptoms while not on neuroleptics. The difference in the severity of symptoms after two years was non-significant; the difference became pronounced in the subsequent years, when there was this difference in medication use. Also the course for these patients off antipsychotics was actually better than for patients with bipolar disorder who were taking a neuroleptic, which also serves as an argument against a positive selection bias.

The authors conclude that the high rate of psychotic symptoms and hospitalizations under maintenance antipsychotic medication suggests that non-adherence to medication might not be the main factor associated with a poor course and outcome. Beyond a basic vulnerability to psychosis, the dose-dependent supersensitivity and augmentation of dopamine-receptors induced by neuroleptics is being discussed as a second causal factor. The authors do not say whether this additional factor applies to the group as a whole, or only to a subgroup.

This is the only existing prospective naturalistic study that addresses the selective use of neuroleptics over a period of [as long as] 20 years. It is a methodologically sound cohort study without randomization. The differences among the comparison groups are significant, and the strength of the effects clinically relevant.

Most of the people in the subgroup without neuroleptics discontinued them against medical advice; there was no guided withdrawal. On the one hand, this accounts for the fact that more people completely discontinued the neuroleptic after the first episode of psychosis than in other existing discontinuation studies (usually 21%) (Emsley et al., 2013). On the other hand, it can also be assumed that not all patients on maintenance neuroleptics actually need them, since they never had an opportunity to attempt a withdrawal.

Whether those patients who stabilized or remitted without neuroleptics might have even needed them initially, and which subgroup (if any) would not have needed them at all, cannot be deduced from this study.

Five randomized or quasi-experimental studies (Bola et al., 2009) have shown that recovery without neuroleptics is indeed possible for around 40% of persons experiencing a first episode within the "schizophrenia" spectrum, as long as they are receiving active milieu-therapy (i.e. Soteria) or early systemic network intervention (i.e. Need-Adapted Treatment). Those findings will be discussed in greater detail below.

The Harrow study illustrates the need for further research and greater availability of alternative treatments in order to reduce long-term neuroleptic use as much as possible among the populations discussed above. For individuals diagnosed with schizoaffective psychosis or transitory psychotic disturbances, there is not sufficient data to come to solid conclusions (Jäger et al., 2007).

4. Transformation of dopamine receptors by neuroleptics

4.1 Loss of drug efficacy over time

Individuals with a diagnosis of "schizophrenia" during their first episode initially experience a reduction of symptoms by greater than 50% within the first 3 months in 52-73% of cases (Robinson et al., 2005; Crespo-Facorro et al., 2006). However, the extent of this remission is only sustained in 23% of subjects for longer than 6 months (Emsley et al., 2007). After 5 years, only 41% (Bertelsen et al., 2008) or 47% (Robinson et al., 2004) display no or only mild residual symptoms (=remission), while all other subjects exhibit much more substantial symptoms.

This diminution in drug effectiveness varies among different neuroleptics. In a post-hoc re-analysis of 5 separate studies on SGAs, Stauffer et al. (2009) determined the proportion of patients who showed a diminishing response rate between 24 and 28 weeks, defined as a worsening of [decline in] the total PANSS score by ≥20%. This re-assessment only included subjects who had shown an initial positive response within the first 8 weeks. Diminished response rates after 24 or 28 weeks varied considerably among different neuroleptics: Olanzapine 5%—17%, aripiprazole 12.5%, risperidone 29%, ziprasidone 29%, and quetiapine 31%. These authors also calculated the number of days elapsed before a drop of 25% in effectiveness would occur. Risperidone, ziprasidone and quetiapine showed such a drop in effectiveness after a period ranging between 96 and 111 days. All of these studies are methodologically hampered by high dropout rates: 46% for olanzapine and 56% for the other SGAs. Realistically, we can assume that the decrease in response rate for those subjects would have been even greater. As an aside, we should note that the studies analyzed by Stauffer et al. were all sponsored by Eli Lilly, and that the authors of this study were employed by Eli Lilly, which produces olanzapine (Zyprexa).

4.2 Forms and effects of transformation of dopamine receptors by neuroleptics

According to current knowledge, the decreasing effectiveness of neuroleptics over time appears to be caused by the drugs' inducing unfavorable compensatory changes and

sensitization at the receptor sites. These changes occur in a dose-dependent fashion; i.e. the higher the dose, the greater the extent of the changes (Samaha, 2008).

The following three types of changes have been described:

1) Within a number of weeks or months, D2-receptors multiply in a counterproductive fashion, a process called "upregulation" (Ginovart et al., 2009), resulting in an average increase of 34% after some months or 70-100% after 16 years of treatment. Individuals with tardive dyskinesia also show a doubling of these receptors (Silvestri et al., 2000). These findings were confirmed in post-mortem studies (Seeman et al., 1987). Therefore, a reduction or discontinuation of neuroleptics tends to free up a larger number of dopamine receptors than were available before initiation of treatment (Silvestri et al., 2000), resulting in greater compensatory excitation and, correspondingly, a resurgence of psychotic symptoms. High-potency FGAs, such as haloperidol, have a greater upregulation-effect than SGAs (Kapur et al., 2001). Risperidone and olanzapine also show this effect, but not quetiapine (Tarazin et al., 2001).

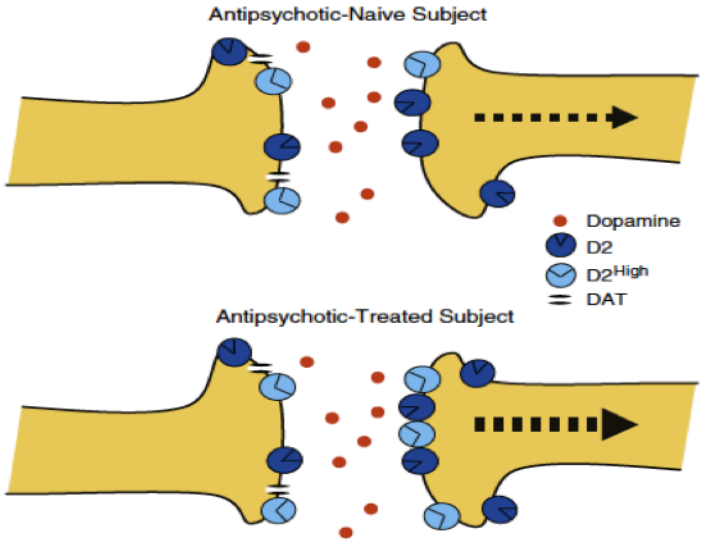

Fig. 8: Dopamine receptor upregulation by antipsychotics. The diagram illustrates how chronic antipsychotic treatment increases the number of dopamine D2 receptors and D2 receptors in a high affinity state for dopamine in the striatum, thereby increasing D2-mediated dopamine signaling (from Samaha et al, 2014, p. 11.)

2) In addition to this effect—possibly with more dire consequences—dopamine receptors are sensitized (dopamine receptor-supersensitivity), resulting in greater responsiveness to dopamine ("D2 high state") (Seeman et al., 2005, 2006; Samaha et al., 2008). Amphetamine, PCP, LSD, alcohol withdrawal and certain brain injuries seem to have similar effects on dopamine-receptors; however, without a concomitant post-synaptic blockade. Therefore, their effects can be observed immediately. The following illustration (Seeman et al., 2006, p. 335) depicts the increased portion of $D2^{High}$ receptors in the striatum engendered by neuroleptics, amphetamines, PCP, genetic transformations and brain lesions in animal experiments. THC (cannabis) shows similar results to quetiapine, but is not included in this diagram. Accordingly, in animal studies the increase of receptors in a $D2^{High}$ state caused by neuroleptics is 100% to 350%. In human subjects, a three-fold increase in sensitivity to dopamine agonists can be detected after multiple years of treatment (Seeman, 2011).

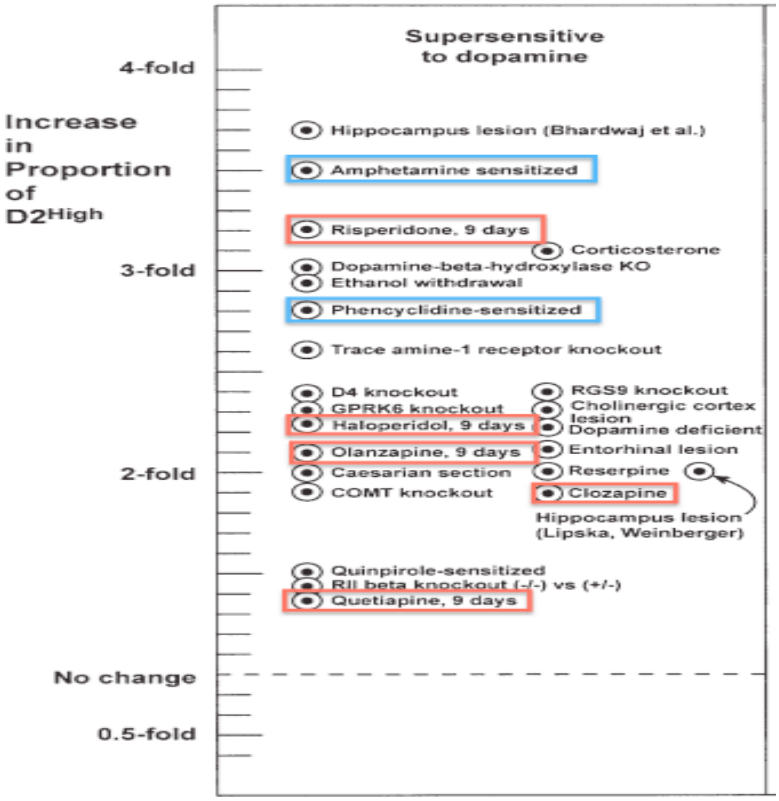

Fig. 9: Dopamine receptor supersensitization from different substances and interventions in rat studies (from: Seeman et al., 2006, p. 335)

3) A blockade of pre-synaptic D2-autoreceptors by neuroleptics leads to an increase in dopamine-synthesis and release (Howes & Kapur, 2009). These three changes at the receptor-site are neuroplastic, i.e. they might be largely reversible with lower dosages or discontinuation. However, such a reversal could take several weeks to months.

The receptor changes lead to the following:

a) A partial loss of neuroleptic effectiveness, resulting in greater (residual) psychotic symptoms in the course of treatment (= neuroleptic-induced partial non-response). In such instances, the receptor changes cannot be fully compensated by a post-synaptic dopamine receptor blockade, even with increasing dosages, which means that symptoms can no longer be sufficiently suppressed (Remington & Kapur, 2010). This can occur within a period ranging from weeks to years, and affects 30-40% of patients.

b) A creeping Increase in dosage over the course of treatment (Seeman et al., 2006). Over time, we see an average doubling of doses, which is even greater in the case of supersensitivity psychoses (see below). In clinical practice, this either involves sensible and compensatory or inappropriate increases ("overshooting"), especially when partial non-response has occurred.

c) Rebound phenomena occurring in the short term as a result of substantial dose reductions or sudden discontinuation (Gardos et al., 1978; Tranter et al., 1998; Moncrieff 2006a, 2006b; Margolese et al., 2002).

d) Supersensitivity psychoses upon reduction of neuroleptic dosages, especially in the case of quetiapine, clozapine and olanzapine (Kapur et al., 2001).

e) An up to 3-fold increase in relapse rates after sudden discontinuation (Gilbert et al., 1995; Baldessarini et al., 1995; Viguera et al., 1997). One small, unreplicated pilot study found a six-fold decrease in relapse rates when the neuroleptic has been withdrawn gradually over 8 weeks, instead of being discontinued suddenly (Green, 1992, cited in Gilbert, 1995).

f) Higher levels of "positive" symptoms in case of relapses (Abi-Dargham et al., 2000; Gur et al., 1998; Grace, 1991)

g) More residual psychotic symptoms after (longer) relapses (Fallon, 2011, 2012)

h) Increased vulnerability to acute psychoses with briefer intervals between exacerbations while taking neuroleptics (Chouinard et al., 1978, 1980; Schooler et al., 1967; Fallon 2011, 2012)

i) Supersensitivity psychoses that occur during stable maintenance dosages, i.e. so-called "break-through psychoses" (Samaha et al., 2007; Weinberger et al., 1981)

j) Could also lead to an increase in substance use among people experiencing psychosis (Samaha, 2014)

k) Severe tardive dyskinesias among patients with the greatest degree of upregulation

The following are indicators of supersensitivity psychoses (Fallon et al., 2012):

- Development of tolerance for neuroleptics, i.e. increasingly larger dosages are required to achieve the same antipsychotic effect.

- Exacerbation of psychotic symptoms within a few days after dose-reduction or discontinuation of neuroleptics, or even while continuing on the same dose.

- Abnormal involuntary movements (AIMs) of the face, lips, jaw, tongue, arms, wrists, hands, fingers, legs, knees, toes, neck, hips and shoulders, without evidence of neuroleptic-induced Parkinsonism with tremor or akathisia (restlessness).

- Greater reactivity to stress, i.e. even mild psychosocial stressors can lead to a worsening of psychotic symptoms or even a full-blown relapse. Stronger psychosocial stressors, i.e. life events, must be ruled out.

Chouinard et al. (1986) determined that supersensitivity psychoses occur at a rate of 22%-43%, depending on the narrowness of the criteria. In two retrospective studies with 128 and 41 subjects, respectively, Fallon et al. (2011, 2012) found rates of 32% and 39% for relapses that met the criteria for supersensitivity psychosis. This group had a higher risk of residual psychotic symptoms and experienced briefer intervals between relapses. Critical life events preceding relapses were much more rare. Another group of 41.5% in Fallon's study showed identifiable life stressors that could be correlated with a relapse; however, these individuals recovered quite well (Fallon et al 2012).

Drug-induced movement disorders (DIMDs), such as Parkinsonism with tremor, rigidity, akinesia, dystonia, dyskinesia and akathisia, are precursors or predictors for the development of supersensitivity psychoses and tardive dyskinesias (Chouinard et al., 1988). An analysis of data from the CATIE and SOHO studies also showed that positive and negative symptoms, as well as anxiety, depression and suicidality, followed the occurrence of DIMDs (Chouinard et al., 2008). SGAs cause DIMDs in 47.4 %– 57.5% of cases.

4.3 Addressing supersensitivity psychoses

When patients experience relapses that take the form of supersensitivity psychoses, the neuroleptic dose should not be increased. The Chouinard group recommends the addition of anticonvulsant drugs such as valproic acid or lamotrigine in such situations. These are said to help in 50% of cases. At the same time, antipsychotic dosages should be reduced to the lowest therapeutic levels, or if possible, discontinued altogether (Chouinard et al., 2008). Another group of authors recommends risperidone depot injections (Kimura et al., 2013), neuroleptics with a longer half-life, or combination with aripiprazole at a very low initial dose and gradual up-titration (Iyo et al., 2013). Experiments with rats provide evidence for a reduction of D2-receptor density under aripiprazole when it had been aggravated by an earlier use of haloperidol (Tadokoro et al., 2012). Ultimately, a very low initial dosage is most likely to reduce or avert the occurrence of supersensitivity psychoses.

A gradual reduction or attempt at discontinuation requires that one make a distinction between symptoms that are due to the withdrawal itself, and those that seem related to the underlying psychotic disturbance, in order to limit maintenance dosages to the actually-necessary minimum. This issue is addressed in greater detail following chapter 9.6 on page 87 of this text. The administration of neuroleptics at two- or even three-day intervals in the event of sustained stability might also limit the undesired up-regulation and sensitization of dopamine receptors without reducing their effectiveness (Samaha et al., 2008). So far, this has been demonstrated successfully in two pilot studies with relatively short follow up (6 months) (Remington et al., 2005, 2010, 2011). Quetiapine and clozapine were not used in these studies, since they are not suited for intermittent use due to their relatively short binding with the dopamine receptors.

4.4 Tardive dyskinesias

Tardive dyskinesias (TDs) are defined as one moderate to severe movement disorder or two mild abnormal involuntary movements (AIM, see p. 41). They are also frequent predictors of supersensitivity psychoses (Chouinard et al., 1990, 2008). Initially, it was assumed that the SGAs had a great advantage when it came to lowered risk for tardive

dyskinesias. However, the most recently published meta-analysis (Correll & Schenk, 2008) reports a relatively high incidence (new diagnoses of TD per year) of 3.9% for SGAs, compared to 5.5% for FGAs.

The six studies that compared the course and outcomes of studies of FGAs only with studies of SGAs only found an average difference, in the incidence of new diagnoses of TD, of 5.5% vs. 4.2%, respectively. Three of these studies actually found no difference in the incidence of TD between first- and second-generation neuroleptics (Miller et al., 2008; Jones et al., 2006; Woods et al., 2010). After taking into account the reversible forms of movement disorders, the TD incidence for FGAs remains at 3% per year (Chouinard et al., 2008). Tardive dyskinesias occur on average in around 30% of all patients (Llorca et al., 2002) and in 42% after more then 5 years of antipsychotic use, without a significant difference between FGA and SGA usage (de Leon, 2006). This increase in TD over time was also noted in a prospective study, reaching 25% after 5 years of exposure to neuroleptics, 49% after 10 years, and 68% after 25 years (Glazer et al., 1991).

A conservative estimate based on the research available in 1986 was 33 million tardive dyskinesia cases worldwide, for 21 million of whom the brain damage was irreversible (Hill, 1986). A 1992 estimate, based on everyone who had ever received the drugs to that date, was 86 million tardive dyskinesia cases, 57 million of which were irreversible (Hill, 1992). The pharmaceutical industry has admitted that tardive dyskinesia is irreversible in 75% of cases (Hill, 1986). The antipsychotic drugs mask the symptoms of tardive dyskinesia in up to 40% of people taking them, so that they only discover the condition if they manage to get off the drugs (Crane and Smith, 1980). It has taken nearly two decades for these disorders to be recognized as a specific result of neuroleptic treatments. The widespread off-label use of SGAs, with a 3-fold increase in prescriptions over 10 years resulting in 3.1 million Americans receiving them in 2011, has led to a greater incidence of tardive dyskinesias than ever before (Cloud et al., 2014). The condition can start to develop within 2 months of neuroleptic treatment (Chouinard et al., 2008). Higher dosages creating a greater D2 blockade also result in a higher incidence of TDs

(Yoshida et al., 2014). Acute extrapyramidal-motoric side effects, which tend to occur above a minimal threshold dose that should not be surpassed, are another predictor for the subsequent development of tardive dyskinesias (Tenback et al., 2006).

5. Further untoward effects and damage caused by neuroleptics

Neuroleptics not only block dopaminergic receptors, but other types of receptors as well. The receptor blockade varies from one neuroleptic to another, and does not necessarily cause significant side effects in a particular individual. Different side effects can occur depending on which receptor type is being blocked. These effects are also dose-dependent. Table 6 shows characteristic side effects that correspond with the blocking of different types of receptors.

Receptor Type	Adverse Effects from Blockade
H1	Fatigue, weight gain
m-Acetylcholine	Visual disturbances, dry mouth, palpitations, constipation, urinary retention, delirium
alpha 1	Drop of blood pressure, dizziness, problems with ejaculation, stuffy nose, tachycardia
alpha 2	Elevated blood pressure, restlessness, anxiety
D2 (dopamine receptor)	Movement disorders, sexual dysfunction, problems with thermoregulation, negative symptoms
5-HT2c (serotonin receptor)	Increased appetite and weight gain
5-HT2a (serotonin receptor)	Fatigue, blood clotting problems
Partial agonist of 5-HT1a receptors	Headache, nausea

Table 7: Side effects corresponding to receptor types

5.1 Reduction of brain volumes

In recent years, there have been a number of studies and meta-analyses that emphasize the risk of a diminishment of gray and white matter of the brain in individuals diagnosed with “schizophrenia,” which can be attributed to the use of antipsychotic medication. This effect depends on the cumulative lifetime dosage of neuroleptics, and is accompanied by adverse effects on cognition and sometimes an increase of negative and positive symptoms. These findings have become considerably more apparent and robust.

Such an effect had already been postulated by at least 1998, when a study by Madsen et al. (1998) published in *The Lancet* suggested that neuroleptics may cause a reduction of frontal lobe volume. In 2011, the long-awaited longitudinal study by Ho et al. appeared, in which 211 FEP patients with a "schizophrenia" diagnosis were followed for an average of 7 years using two or more MRI exams. Even after controlling for length and severity of illness as well as substance abuse, there was evidence for a reduction in frontal, temporal, parietal and total grey matter that correlated positively with the cumulative neuroleptic dose. In addition, there was a reduction in white matter which correlated with cumulative moderate or higher dosages of neuroleptics. Surprisingly, the greatest loss of grey matter occurred at the onset of treament, while the reduction of white matter progressed over time. This loss of brain matter was associated with neuropsychological deficits (Andreasen et al., 2013). The only difference between SGAs (with the exception of clozapine) and FGAs in this study was that higher SGA doses were significantly associated with larger parietal WM volumes and lower parietal GM volumes. Concerning the validity of these findings, Andreasen gave this comment in the *New York Times* several years before the publication of the study:

> ″The reason I sat on these findings for a couple of years was that I just wanted to be absolutely sure it was true. My biggest fear is that people who need the drugs will stop taking them." (Andreasen, 2008).

> And Ho pointed out later: "We have been looking at the data for five years. We've been very careful to get it right because of the potential implications . . . . It's not the ideal study design, but it is as good as we could ever get with something like this." (Cyranosky, 2011).

In the most recent publication of data from this study, Andreasen et al. (2013) reported correlations between the length and number of relapses and the total and localized brain volumes, in addition to cumulative antipsychotic dosages. The antipsychotic dosages as well as the duration of relapses—but not the frequency of relapses—correlated with the reduction of frontal white matter volumes, even after controlling for other co-variables.

The amount of reduction after one year was double in size related to relapse compared to reduction related to neuroleptic use. Relapses of shorter duration did not correlate with brain volume reductions. However, unlike the earlier publication (Ho et al., 2011), this analysis did not take the differences among cumulative dosages into account. Instead, they only used one average daily dose equivalent to 4 mg haloperidol. This represents a departure from the earlier study, where dosages continued increasing from 4 to 11 mg haloperidol-equivalents over time with good treatment adherence. Cumulative dosages for individual subjects would have been available for inclusion in the analysis, but were not used. The authors do not explain why they chose these average daily dosages, which are divergent from the earlier study and methodically inconclusive. The average length of relapse was 1.34 years, although many subjects had considerably briefer relapses. There was no significant impact across the average length of follow-up (7 years) between the number of relapses and any reduction of brain volume. Briefer relapses do not appear to have adversely affected brain volume. These findings provide considerable support for a strategy of guided dose-reduction and discontinuation, as employed in the recent longitudinal study by Wunderink et al. (2013). We will address this study in greater detail below. To leave clients who understandably advocate for dose-reduction and withdrawal to their own devices, thereby increasing their risk of losing all professional supports and developing a protracted relapse, seems quite negligent.

A multicenter study by Lieberman et al. (2005) of first episode patients—financed by Eli Lilly—caused a stir with the finding that haloperidol (N=79) resulted in a significantly greater reduction of frontal grey matter at the 3- and 6-month assessments than olanzapine (N=82). However, this difference was no longer significant after one year: a 2.4% reduction for haloperidol and a 1.0% reduction for olanzapine. The dosages of haloperidol and olanzapine used in this study were actually not equivalent, thus hindering a proper comparison. After an initial increase in whole brain and frontal GM volume within 12 weeks under olanzapine, the reductions of volumes under olanzapine and haloperidol converged in the course of the subsequent follow-up period. Grey matter brain changes showed no relationship to the daily dose. Unfortunately, the total cumulative dose was not determined. It is unlikely that such short term GM increases

were caused by the appearance of new neurons or connections (Molina et al., 2005). Such volume increase can be a withdrawl effect from FGA after pretreatment with these substances in 77% of the individuals over 4 weeks (Molina et al., 2005; McClure et al 2006) and might also be caused by changes in blood circulation, fat and water content which can be caused by neuroleptics (Joober et al., 2006).

Less well known than that original haloperidol vs. olanzapine study is a re-analysis of the complete data set, including all four follow-up points from one of the imaging centers used in the study. This reanalysis was performed to get a more accurate picture of the grey matter changes over time as related to the medications, and to address any possible distortions of the data due to the use of several different MRI scanners (Thompson et al., 2009). According to this reassessment, the loss of grey matter ran in different trajectories for these two medications. After one year and an adequate correction for multiple comparisons among all examined regions, there were again no differences between haloperidol and olanzapine. It appears that any apparent differences between these two drugs had been transitory. Due to the many dropouts, this study cannot provide information about the further course beyond 12 months.

A recently published meta-analysis of 8 long-term studies with a total of 629 subjects diagnosed with "schizophrenia," who had experienced multiple episodes and were followed for an average length of 72 weeks, once again confirms an early onset of brain volume reduction under neuroleptic treatment (Fusar-Poli et al., 2013) even after controlling for length of illness and severity of psychotic symptoms, among other factors. There was a correlation between the total degree of grey matter loss and higher cumulative doses of antipsychotics. Overall effect size was small to medium (patients: − 0.25 and control group: − 0.14).

The group-level analysis could not rule out the possibility that these pathological changes might only occur in a subset of "schizophrenia" patients. A meta-analysis could not test the hypothesis that the changes in brain volume might be nonlinear (greatest at the

beginning of the illness). No assessment of potential differential effects of FGA vs. SGA was conducted.

Another meta-analysis included 43 studies (Radua et al., 2012) with a total of 965 first-episode patients. Whole brain structural and functional imaging studies employing cognitive tasks, assessing which brain regions showed both structural and functional abnormalities in subjects with a FEP, were included in this meta-analysis. A number of potential confounding factors were controlled, including exposure to antipsychotics. Only brain regions where a functional response in neurocognitive tests could be discerned were analyzed, in order to avoid the inclusion of volumetric changes without clear functional correlates. The following brain strucutures showed reductions of gray matter along with cognitive decline: medial frontal area, anterior cingulum and insula. Among patients treated with antipsychotic medications the effect sizes were small to medium (between – 0.18 and – 0.37). A similar but much smaller reduction was also observed in patients without neuroleptics, with effect sizes between -0.02 and -0.15. The anterior cingulum is relevant for the integration of emotional and cognitive processes, and executive, social cognitive and affective functions. Known insula functions are integration of external sensory input, awareness of body states, processing of visual and auditory emotional information, bodily hallucinations and neuronal representations of the self. The major limit of this study was a selection bias due to the fact that patients who were relatively well could be scanned in the absence of neuroleptic treatment, while patients on antipsychotics tended to have more symptoms. Uncontrolled confounders were severity and duration of illness, as well as tobacco, cannabis, and alcohol use.

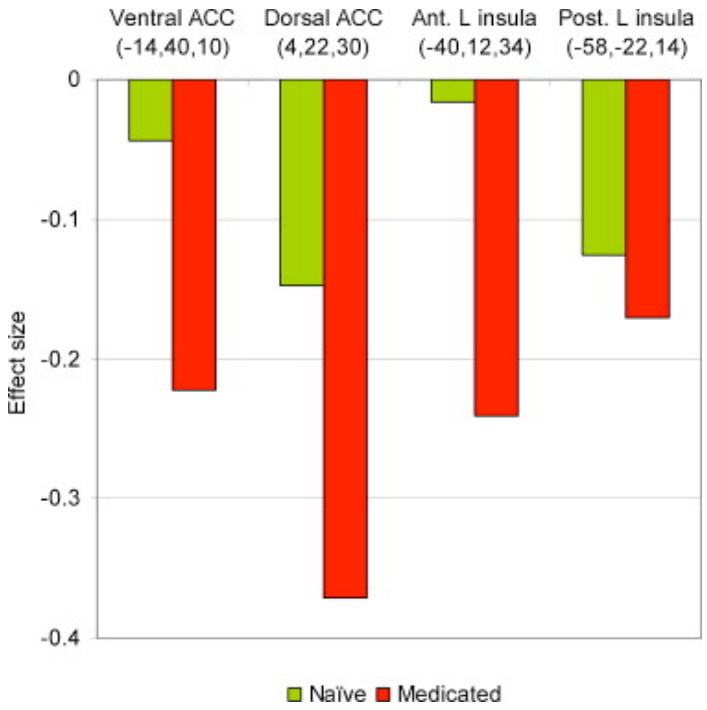

Fig. 10: Effect size of the differences in grey matter volume between antipsychotic-naïve patients and controls (green bars), and between medicated patients and controls (red bars), in the four peaks of multimodal abnormality in anterior cingulated cortex (ACC) and left insula. No differences between naïve and medicated patients were found in the right insula (from: Radua et al., 2012, p. 2329).

Another systematic review of 10 identified outcome studies concerning the frontal lobe (Aderhold et al., 2014) found evidence for brain volume reduction under neuroleptic treatment. Length of interscan interval was 1 to 7 years. Four out of six studies of first-episode patients under FGAs found reductions of frontal volume in correlation with the cumulative neuroleptic dose (Cahn et al., 2002; Ho et al., 2007; Ho et al., 2011) or with the average daily dose (Gur et al., 1998). Similar results were found for patients treated with SGAs in 4 of 7 studies.

Two out of four studies of multiple episode patients under FGAs, and one of two studies under SGAs, found a frontal grey matter volume or cortical thickness reduction in correlation with the cumulative neuroleptic dose (Ho et al., 2011). One study showed a smaller decrease of frontal grey matter under clozapine (van Haren et al., 2011) and olanzapine (van Haren et al., 2007), but without any correlation to clinical outcomes.

However, the left superior temporal lobe showed greater cortical thinning under Clozaril, which correlated with poor clinical outcome.

Some of the newer studies included in this review emphasize that these changes appear to begin during the first weeks of treatment. Five of these studies provide evidence for a correlation between atrophy of frontal and temporal grey matter over time and certain cognitive disturbances (attention, executive functioning, verbal learning, working memory, problem solving ability, abstract flexibility, spatial memory, and visual-spatial abilities). The greater the reduction in grey matter volume, the more pronounced these cognitive deficits. After an initial deterioration followed by a period of relative stability between the second and fifth year of neuroleptic treatment after the onset of illness, there appears to be another period of further significant deterioration of cognitive functioning between the fifth and ninth year, whose relationship to medications has not been determined (Andreasen et al., 2005). Correlations with more positive or negative symptoms or increased social needs were also found in 5 studies.

Currently, it cannot be determined with certainty whether second-generation antipsychotics are associated with a relatively lower reduction in brain volume than FGAs. One study where subjects were treated with low doses of FGAs or SGAs over one year did not find differential effects concerning cortical grey matter and "cortical thickness" (Crespo-Facorro et al., 2008; Roiz-Santiáñez et al., 2012). Studies with monkeys demonstrate similar but greater effects without a difference between haloperidol and olanzapine (Dorph-Petersen et al., 2005; Kopanokaske et al., 2008). The following mechanisms concerning the impact of antipsychotics on increased atrophy of the brain are debated:

- Fronto-mesolimbic disconnection through D2 blocking (Ho et al 2011), in particular the reduction of psychotic symptoms through D2-receptor blockade in the basal ganglia, which is associated with a reduction of information-processing in frontal, striatal and thalamic regulatory networks (Heinz et al., 2010)

- Decrease of activation in the dorsolateral frontal cortex and anterior cingulum (Keedy et al., 2009)

- Chronic frontal hypoperfusion (Ho et al., 2011)

- Neurotoxicity via oxidative stress and caspase-3-activation (Wang et al., 2013; Ukai et al., 2004; Jarskog et al., 2007) which can lead to:

  a) decreased density of dendrites (Dean et al., 2006; Nasrallah, 2013)
  b) decreased number of glia cells (Kopanokaste et al., 2008)
  c) cerebral cell death/apoptosis (Post et al., 2002; Bonelli et al., 2005)

There is evidence for the following neurotoxic effects of haloperidol: apoptosis, necrosis, reduced cellular functionality, inhibition of cell growth, elevated Caspase-3-activity, interference with glutamate transport, and damage to mitochondria (Nasrallah, 2013). Nine out of 28 studies are older than 12 years. The first studies were published in 1996, shortly after the introduction of the first SGAs. SGAs do seem to have advantages, according to animal studies. However, in most human imaging studies concerning the atrophy of grey and white matter, the differences beween FGAs and SGAs are negligible.

In sum, there is increasing evidence from recent studies that neuroleptics can aggravate the moderate illness related structural brain changes during its course (Zipursky et al., 2012) by inducing further small to moderate changes, including GM and WM volume reductions, especially in the frontal lobes. Such a reduction appears to affect white matter under moderate to high dosages in a slowly progressive manner (Ho et al., 2011).

5.2 Cognition and neuroleptics

Cognition encompasses, for example, working and verbal memory, attention, processing speed, executive functioning, problem solving and logical thinking, which are all functions of the pre-frontal cortex. Studies utilizing complex neuropsychological tests

have demonstrated mild to moderate cognitive deficits among 75% of individuals diagnosed with "schizophrenia" (Palmer et al., 1997; Kremen et al., 2000).

Comparisons between a subgroup of highly functioning persons diagnosed with "schizophrenia" and similarly functional "healthy" individuals shows a difference in working memory capacity of less than 10%, while the lower functioning groups with such a diagnosis differ by 16% from a lower functioning healthy comparison group. These patients took a regular maintenance dose of FGAs or SGAs (Callicott et al., 2003). These limitations seem to be caused by permanent deficits of dopaminergic transmission at the D1-receptor (Shlifstein et al., 2015) as well as changes in the glutamate-system of the prefrontal cortex (Poels et al., 2104). The duration of untreated psychosis (DUP) has no influence on the levels of cognitive dysfunction, which contradicts the supposition of neurotoxic effects caused by acute psychoses (Perkins et al., 2005; Rund et al., 2007; Goldberg et al., 2009).

To this day, it remains controversial whether neuroleptics on their own might have "pro-cognitive" effects, or whether any observed improvements during acute treatment might simply be caused by a reduction in psychotic symptomatology or by learning effects from frequent retesting. Carpenter & Gold (2002) discuss the myth that neuroleptics alone could improve neurocognition. Their basic assumption is that neuroleptics might cause further deterioration of already limited cognition in a dose-related fashion, and that additional anticholinergic drugs, primarily used in conjunction with FGAs, would further aggravate this effect. These unfavorable effects are easy to conceal, due to the fact that cognitive tests pre- and post acute psychoses are likely to improve simply as a result of improved reality orientation, lessened disorganization, and training effects when retaking the same tests. These improvements mask the limitations caused by neuroleptics.

Neuroleptics aggravate cognitive functioning through their negative impact on motivation, affect, attention, energy levels, and motor retardation. In addition, there are limitations related to working memory and anticholinergic effects. Whenever atypicals (SGAs) have less of a negative impact in these areas, this might be considered an

improvement in neurocognition rather than merely a lessening of these side effects. A directly favorable effect of SGAs on cognition has not been observed by these authors.

There are few randomized, well-controlled studies of sufficient size that account for the influence of acute symptoms, medication and training effects on cognitive functioning. Nevertheless, even considering the limited degree of quality research, there are several studies that provide evidence for a contingency between cognitive functioning and acute psychotic symptoms (Strauss, 1993 review; Pigache, 1993; Servan-Schreiber et al., 1996; Censits et al., 1997). More recent imaging studies have shown a significant correlation between the intensity of acute symptoms and prefrontal dysfunction in the case of disorganization (Perlstein et al., 2001), formal thought disorders (Assaf et al., 2006), delusional thinking (Menon et al., 2001) and hallucinations (Fu et al., 2005). Therefore, it seems reasonable to assume that an amelioration of acute symptoms is associated with an improvement in cognitive functioning.

As already mentioned, most cognitive tests are associated with learning effects, suggesting that repeated testing results in improved performance, which is often misinterpreted as an improvement of cognition related to neuroleptic treatment. Such training effects have to be accounted for whenever improvements are noted, and, on the other hand, any lack of improvements on these tests that are sensitive to training effects should be interpreted as a neuroleptic side effect.

Further possible adverse effects on neurocognition can be deduced from their immediate effects on various receptor systems:

> a) A direct blockade of frontal D1 receptors, with the exception of amisulpride (a selective D2-antagonist) and clozapine (a partial D1-agonist, which might explain some of the particular effects of this drug) (Abi-Dargham et al., 2003).

b) A dose-dependent down-regulation of D1 receptors, particularly in the frontal and temporal cortex (Lidow et al., 1994; Hirvonen et al., 2006), which is presumably caused by D2 blockade and therefore associated with all neuroleptics (Lidow et al., 1997).

c) Anticholinergic effects associated with many neuroleptics (e.g. clozapine, olanzapine, quetiapine, low-potency typicals), as well as with anticholinergics given for Parkinsonian symptoms and early dyskinesias (biperidene, trihexphenidene) and a variety of antidepressants (these effects are greater for TCAs like amitriptyline, imipramine, doxepine, nortriptyline than for SSRIs like fluoxetine, citalopram, fluvoxamine, and paroxetine).

d) A mid- to long-range reduction of grey and white matter in frontal and other brain regions, dependent on the cumulative neuroleptic dose.

e) An overall reduction of frontal metabolism under neuroleptic treatment (Holocomb et al., 1996; Keedy et al., 2009).

The evaluation of data from 440 subjects who participated in the CATIE study and took risperidone, olanzapine, or ziprasidone resulted in a dose-related worsening of alertness, working memory, processing speed, verbal memory, and abstract-logical thinking, especially beyond a D2-receptor blockade of 77% (Sakurai et al., 2012). At least 10 additional studies confirm a deterioration of cognitive function with increasing dosages (Cassens et al., 1990; Sweeny et al., 1991a, 1991b; Bilder et al., 2000; Harvey et al., 2001; Albus et al., 2002; Moritz et al., 2002—looked only at *FGAs;* Green et al., 2002; Forbes et al., 2009; Sponheim et al., 2010).

The adverse effect of SGAs on cognitive functioning due to an additional unintended blockade of acetylcholine receptors was also investigated (Vinogradov et al., 2009). This study with 49 subjects shows a substantial negative impact related to the anticholinergic

effects of certain SGAs (clozapine, olanzapine, quetiapine). These anticholinergic effects of certain psychopharmacologic agents diminished the overall impact of a computer-supported cognitive training program by 20%. Verbal working memory, verbal learning and several other memory components within the assessed domains were adversely affected. On the other hand, patients treated with typical neuroleptics who had more positive symptoms showed 20% better results from the cognitive training program (50 hours) than those subjects who took drugs with greater anticholinergic side effects. Dosage and type of substances in the patient group with high serum anticholinergic activity were the following: clozapine 800 mg, olanzapine 20 mg, quetiapine 800 mg, haloperidol 20 mg, valproic acid 1000 mg, lithium 450 mg, gabapentin 600 mg, lamotrigine 100 mg, olanzapine 20 mg, mirtazapine 30 mg, and trazodone 150 mg. The authors emphasize that the patients who experienced the least pronounced anticholinergic side effects while being treated with "more conservative" medications (i.e. typicals) performed better in cognitive training, even though they showed more positive symptoms, than patients with greater anticholinergic side effects.

Furthermore, Vinogradov and co-authors acknowledge that their study most likely selected participants who had better cognitive functioning in general, due to the complexity of the intervention. Patients who received even higher dosages due to "treatment resistance" presumably showed even greater levels of dysfunction. They also emphasize that cognitive functioning is very important for integration into vocational settings, and correlates positively with the effectiveness of rehabilitative interventions. There are no studies assessing the relationship of neurocognition to the effectiveness of psychotherapeutic interventions (Vinogradov et al., 2009).

A study of 42 patients during a first episode of "schizophrenia" (Faber et al., 2012) showed an improvement on tests related to attention, cognitive speed and flexibility, working memory, speech fluency, verbal learning and abstract reasoning while neuroleptics were being reduced (N=10), and even more substantially upon their discontinuation (N=12). This result is also confirmed in a study of 61 stable patients diagnosed with "schizophrenia" whose dosages had been reduced by 50% to 5 mg of

olanzapine or 2 mg risperidone (Takeuchi et al., 2013). There were improvements of language-related cognitive functions and extrapyramidal side effects without any worsening of psychotic symptomatology. A recent naturalistic outcome study followed 40 individuals born in the same year who had received a diagnosis of "schizophrenia" or "schizophrenia spectrum disorder" over a period of nine years, between the ages of 35 and 43. A comparison with healthy controls revealed poorer results early on in a test of verbal learning and memory (California Verbal Learning Test – CVLT) among the sub-group receiving higher annual dosages of neuroleptics (Husa et al., 2014). Since it is possible that this is merely a function of more severely ill patients receiving higher dosages, the study controlled for severity, length of illness, and days spent in the hospital. Nevertheless, the effect remained significant at moderate to high levels. Furthermore, there was a progressive, but less significant limitation in immediate free recall for the group that received higher annual dosages, which had not shown any differences in the earlier phase of the study. There were no differences on these tests between various neuroleptics. The influence of other confounding variables on this cognitive deterioration cannot be excluded with this study design.

After SGAs had been assumed to be more favorable for cognition and marketed as such over many years, studies that used equivalent dosages of FGAs and SGAs began to reveal sobering results (Green et al., 2002). According to the CATIE study (Keefe et al., 2007), the effects of various neuroleptics on cognition were not significantly different. However, with perphenazine (an FGA), cognition was significantly better after 18 months than with olanzapine or risperidone. While there might be modest advantages for certain SGAs over the first few months, these are not sustained beyond one year (Keefe et al., 2006). One meta-analysis reported a slight advantage for SGAs, while more recent studies show even smaller differences. When it comes to clinical decisions, these differences are trivial (Faber et al., 2011). The decisive factor for both the SGAs and FGAs is to use the the lowest possible dosage.

A study by Moritz et al. (2013) found significant adverse effects on subjective experiences under neuroleptics. They reported three factor-analytic clusters:

(a) self-doubt, experiencing oneself as a different person, difficulties in decision-making, depressed mood

(b) cognitive and emotional blunting, impoverished fantasy, cognitive and emotional dulling, poor perception of external stimuli, difficulties in visualizing problems

(c) social withdrawal

Similar subjective responses were also seen in individuals being treated with neuroleptics for non-psychotic problems, thus suggesting that these are not illness-specific effects.

5.3 Obesity, metabolic syndrome and diabetes, cardiovascular diseases, sudden cardiac death

There is a fundamentally greater risk for the incidence or aggravation of these somatic illnesses under neuroleptic treatment (de Hert et al., 2011a). For example, depending on the study, there is a 15-72% incidence of drug-induced weight gain (de Hert et al., 2011a). Forty percent to 50% of patients receiving long-term neuroleptic maintenance medication suffer from a metabolic syndrome (Correll et al., 2006). This risk is greatest with clozapine, olanzapine, quetiapine and risperidone, in descending order, as well as with polypharmacy. Smoking, inactivity and nutrition should be considered additional risk factors.

A study of 394 individuals experiencing a first episode of psychosis (FEP) determined the following effects after an average of 47 days of neuroleptic treatment (93.5% with SGAs) (Correll et al., 2014). Antipsychotic treatment duration correlated significantly with:

- Elevation of non-HDL-C trigycerides
- Elevated triglyceride/HDL ratio (early indicator for insulin-resistance)

- Lowering of protective HDL-C
- 15.4% of the subjects already showed signs of pre-diabetes, as defined by HbA1c levels.

Clozapine and olanzapine were associated with the greatest metabolic risks. Quetiapine had only a somewhat lower associated risk, leading the authors to suggest that its first-line use in first-episode psychosis may need to be reevaluated.
Furthermore, while 3% were already diabetic, as many as 15.4% had HbA1c-defined prediabetes, which has an 8-year risk for diabetes comparable to fasting glucose–defined prediabetes. "Of concern regarding future diabetes risk, the HbA1c-based prediabetes frequency (15.4%) was already 70% of that observed in patients with chronic schizophrenia (21.6%) who were 16 years older" (Correll et al., 2014 p. 1560).

Another review of first episode psychosis (FEP) studies with at least six-month duration (Foley et al., 2011) showed that even in such a short time-span, the rates of weight gain, obesity and elevated BMI nearly doubled. No significant differences between the various drugs were noted. The chance of reversing the weight gain over a longer period by switching from one neuroleptic to another seems small (Bak et al., 2014). In the presence of a metabolic syndrome (at least 3/5 of the following: weight gain, hypertension, lipid dysregulation, glucose-tolerance, insulin-resistance), the risk of heart disease is doubled after two years (Correll et al., 2006). The mortality-rate from heart disease rises by a total of 3.6 times (de Hert et al., 2011a) in a dose-related fashion (Osborn et al., 2007).

Neuroleptics—especially olanzapine, clozapine, quetiapine and Risperdal less so, but also low-to mid-potency FGAs—can result in a greater incidence of pre-diabetes (37%) and type-2 diabetes (10%), depending on the increase of waist circumference, metabolic syndromes, and lipid dysregulation (Sernyak et al., 2002; Manu et al., 2012; Stahl et al., 2009; Mitchell et al., 2013). A 10-year retrospective cohort study of clozapine showed new onset of diabetes in 34% of the patients (Henderson et al., 2005). The risk for diabetes rises in a dose-dependent fashion, as well as in association with polypharmacy (Citrome et al., 2004; Correll et al., 2007). In 25% of the patients, diabetes develops

without weight gain due to direct effects of neuroleptics on insulin metabolism (Jin et al., 2004). In 60% of the patients who eventually become diabetic, this becomes apparent during the first six months of treatment (Koller et al., 2001, 2002, 2003). Therefore, regular and initially frequent monitoring of fasting glucose levels is necessary in all patients, but especially those on higher-risk neuroleptics, in particular because an incipient diabetes might be reversible by changing the medication. A determination of Hb A1c hemoglobin, along with fasting blood sugar, seems to be the best screening procedure (Manu et al., 2012). 30% of patients taking atypicals exhibit elevated FBS, even if they do not have a history of diabetes (Sernyak et al., 2005). This early metabolic change goes along with an elevated risk for cardiovascular morbidity (Gerstein et al., 1999; Coutinho et al., 1999). A metabolic syndrome that includes diabetes has a 7.7 times higher risk of cardiovascular morbidity (Correll et al., 2006).

Sudden cardiac death in patients diagnosed with "schizophrenia" occurs twice as often as in the general population. The risk of sudden cardiac death increases during neuroleptic treatment in a dose-dependent fashion, by anywhere from 1.5 to 2.8 times (Ray et al., 2009). FGAs and SGAs appear to carry approximately the same risk (Ray et al., 2009). Individual substances do involve varying increases in risk, however, ranging from 1.7 to 5.3-fold (de Hert et al., 2011a). After 30 years of taking neuroleptics, the sudden-death rate associated with these drugs can be estimated at 4.5%, even though the annual incidence is rather small. Serious cardiovascular morbidity can increase this risk up to 95-fold, according to one study (Ray et al., 2001). Neuroleptics combined with other substances such as antidepressants (tricyclic, tetracyclic, SSRIs, venlafaxine), lithium as well as antibiotics, anti-arrhythmics, and antihistamines, increases this risk even further, calling for additional ECG-monitoring in certain high-risk patients. ECG studies should generally be conducted according to the frequency listed in the guidelines, but in high-risk patients even more frequently. A QTc-interval greater than 500 msec calls for a change in medication regimen.

5.4 Shortened life expectancy

A systematic review of outcome studies that were largely conducted prior to the introduction of SGAs has already pointed to a contribution by neuroleptics to the dramatic reduction of life-expectancy by 13 to 30 years for individuals with psychotic disorders, in addition to other factors such as smoking, lack of exercise, poor nutrition and inadequate medical care (Weinmann et al., 2009, de Hert et al., 2011).

The publication of a large Finnish population-register study over 11 years, which apparently provided proof for higher mortality among untreated individuals in comparison to patients on neuroleptics, threw a monkey wrench into this discussion (Tiihonen et al., 2009). Unfortunately, a comprehensive, 7-page methodological critique of this study did not receive equally widespread attention. The main problem of varying time periods for recruitment of the historical cohort and limited availability of prescription data cannot be solved through statistical analysis. Beyond a variety of methodological deficiencies, some of the most important problems with this study are the fact that 64% of deaths in patients treated with antipsychotic medications were not taken into consideration when comparing the mortality rates of current use of different neuroleptics because patients' deaths during hospitalization for longer than 2 days were excluded. Furthermore, the group of patients without neuroleptics who died sooner during the study period seemed to be considerably older on average than the patients in the entire study, with an average age of 51. Oddly enough, the table showing the age ranges of the non-medicated group is missing in this publication and the age effect for this group is selectively not mentioned in the supplementary material. This 'no antipsychotic drug' group had a total number of 18.914 individuals (28% of all included patients) and 8277 of them (i.e. 43%) died during the assessed follow up time of 7.8 years, which was in fact shorter than the 11 years mentioned in the title of the study. This equals an annual mortality rate of 5.6%. Another Finnish study by Salokangas et al. (2002) - mentioned by de Hert et al 2010 - found in four different cohorts covering 1982–1994 a mean mortality rate of 5.2% for three years, or an annual mortality rate 1.7%. The reasons for the much higher mortality rates found in this study are not discussed and remain unclear. Also, the effects of length of illness and earlier treatment with

neuroleptics were only controlled for with the 11 years of available data, but not the 23 previous years when people might have already been taking neuroleptics (de Hert et al., 2010). In our opinion, it is not fair to cite this study without mentioning de Hert's critique of its methods, and yet this is how the Finnish study is routinely referenced in other studies. (e.g. Deutschenbaur et al., 2014).

A more recent editorial in the Lancet (2011), where the Finnish study was originally published, reads like a corrective:

> Nevertheless, there is a large health gap between patients with severe mental illness and the general population, and consistent evidence of increased cardiovascular mortality with antipsychotic treatment. The combination of antipsychotic side effects with poor diet, physical inactivity, high rates of smoking, and other factors associated with psychotic illness, together with socioeconomic deprivation, has a devastating effect on cardiometabolic health. It is no surprise, therefore, that people with severe mental illness have lives 16–25 years shorter than does the general population, and that coronary heart disease, not suicide, is the major cause of death . . . In any other scenario, the responsible physician's response would be to seek an alternative. However, for mental health professionals, the mainstay of treatment for psychotic illness is—as it has been for over half a century—antipsychotic medication. (Lancet, 2011 (377), p. 611)

Approximately 33% of deaths in the general population are due to coronary artery disease, in comparison to 50-75% among patients with a diagnosis of "schizophrenia" (Hennekens et al., 2005). Most SGAs, but also some FGAs, raise the risk of cardiovascular morbidity and mortality (De Hert et al., 2009; Cohen & Correll, 2009; Correll et al., 2009; Meyer, 2001). Peter Götzsche, a founder of the Cochrane Collaboration, which is engaged in the production of critical meta-analyses, comes to the conclusion that Eli Lilly Co. killed approximately 200,000 people with olanzapine ("Lilly has killed") based on the current state of research, even if only every 100th patient had

died from causes linked to the effects of this substance. Worldwide, approximately 20 million people have been treated with olanzapine, frequently for "off-label" indications, i.e. without formal approval of its use for these conditions. Considering the high metabolic, cardiovascular and diabetic risk associated with this substance, this is a rather conservative estimate (Götzsche, 2014, p. 269).

Beyond these problems, there are other significant side effects such as sexual and menstrual dysfunction, osteoporosis, and malignant neuroleptic syndrome. Finally, stigma-promoting side effects such as dry mouth and bad breath, hirsutism and facial hair in women, acne, tics, and incontinence are not taken seriously enough (Seeman, 2011).

6. Neuroleptic use in different age groups

6.1 People over 40

People over 40 experience particularly strong side effects. A 2-year follow-up study of 332 patients over 40 with psychotic symptoms and a diagnosis of "schizophrenia", bipolar disorder, PTSD and dementia, assessed the effects of aripiprazole, olanzapine, risperidone and quetiapine over a mid-range period of time (Jin et al., 2012). Patients or clinicians were allowed to refuse one or two of these medications, and were then randomly assigned to one of the other drugs. In this manner, 83% of patients could be enrolled in the study who might have been excluded from other studies. Dosages were relatively low, and the results were generally independent of the diagnosis. The sub-group on quetiapine had to be terminated prematurely due to a high rate of severe side effects (38.5% vs. 19% of the subjects for the other atypicals). The average length of time until the randomized medication was discontinued prior to the end of the 2-year follow-up period was 26 weeks. This early discontinuation occurred for quetiapine in 78% and for aripiprazole in 81% of the patients, a non-significant difference. These discontinuations of treatment were independent of the diagnoses and 52% occurred due to side effects. Twenty-four percent of all patients developed severe side effects (including death, hospitalizations and emergency room visits for life threatening

conditions), 51% had non-serious adverse events. There were no significant differences among the various neuroleptics in the occurrence of metabolic side effects. Half of the entire sample did not have a metabolic syndrome at the beginning, but 36.5% of these patients developed such a syndrome in the course of the study. The authors conclude:

> Caution is advised for a prolonged use of these substances beyond age 40. They should be given only in low dosages over a short period of time, along with careful monitoring of side effects. It is recommended that patients and their relatives/supporters participate in a discussion about the pros and cons of atypical neuroleptics and any possible alternatives in order to arrive at a joint decision. (Jin et al., 2011, p.11)

6.2 Neuroleptics for children and adolescents

In Germany and other Western countries, prescriptions of neuroleptics for children and adolescents are rising continually. According to data from the largest German health insurance company (AOK), prescriptions of risperidone for youth 10 to 15 years rose 36-fold between 2001 and 2006. Prescriptions of risperidone for those 15 to 20 years old rose 2.7-fold during this period. In the United States, the number of office-based visits by youth that included antipsychotic treatment increased six-fold from 1993 to 2003. The researchers determined that only 14% of the pediatric prescriptions of antipsychotics, in the most recent period, were to treat psychotic disorders; instead they were being prescribed primarily for disruptive behaviors, mood disorders, developmental disorders and mental retardation (Olfson, 2006).

The largest publically funded, double-blind, randomized multi-site study (TEOSS) included 116 teenagers (75% below 16 years old) diagnosed with early onset schizophrenia and schizoaffective disorder who received acute treatment with either olanzapine (2.5–20 mg/day), risperidone (0.5–6 mg/day), or molindone (10–140 mg/day, plus 1 mg/day of benztropine) for 8 weeks. It found only modest effects on positive symptoms from olanzapine, risperidone and molindone. Response was observed in 50%

of subjects treated with molindone, 34% of subjects treated with olanzapine, and 46% of subjects treated with risperidone; a non-significant difference. The mean reduction in psychotic symptoms was modest, ranging from 20-34% in the PANSS. Across all three treatments, more than half the participants failed to achieve an adequate response after 8 weeks of therapy. The response rates were generally lower than those reported in studies of young adults with first-episode schizophrenia using similar criteria. Fewer than half of the subjects were even able to complete the first 8 weeks of treatment. The researchers wrote:

> Adverse effects were frequent but differed among medications. The results question the nearly exclusive use of second-generation antipsychotics to treat early-onset schizophrenia and schizoaffective disorder. The safety findings related to weight gain and metabolic problems raise important public health concerns, given the widespread use of second-generation antipsychotics in youth for nonpsychotic disorders. (Sickich et al., 2008, p. 1420)

Fewer than half of these patients (N=54) entered a maintenance treatment trial lasting 44 weeks (Findling et al., 2010). Fourteen (26%) completed 44 weeks of treatment. Adverse effects (n = 15), inadequate efficacy (n = 14), or study non-adherence (n = 8) were the most common reasons for discontinuation. Thirty-nine percent discontinued treatment within 8 weeks of an acute phase, and 88% within one year. Therefore, only 12% of the participants completed the study. The three treatment arms did not significantly differ in symptom decrease or time to discontinuation. In contrast to the antecedent 8-week acute trial, there were no significant differences between treatment groups in change of weight, BMI, BMI percentile, or BMI adjusted for age and sex during the maintenance phase. However, patients treated with olanzapine did maintain significant increases in adjusted weight and BMI scores over those taking molindone during the entire 52-week study. The study arm of subjects receiving olanzapine was prematurely terminated by the ethics committee due to a weight gain of 13.5 lbs. on average.

Another randomized study of atypicals in 505 children and adolescents revealed a weight gain of 8-15% within the first 11 weeks on olanzapine, risperidone and quetiapine (Correll et al., 2009). Weight increased by 8.5 kg with olanzapine, by 6 kg with quetiapine, by 5.3 kg with risperidone, and by 4.4 kg with aripiprazole compared to a minimal weight change of 0.2 kg in the untreated comparison group (n=15). The percentage of patients gaining 7% of their initial weight or greater were 84 % for olanzapine, 55 % for quetiapine, 64 % for risperidone, and 58 % for aripiprazole. The findings for youth and adult populations converge, in that body weights and metabolic indices were similar to norms for the respective general population prior to treatment and cardiometabolic abnormalities started to emerge early during antipsychotic exposure. Considering that there was an untreated comparison group, it is not likely that these changes were a result of the newly diagnosed psychiatric disorder or of hospitalizations. The authors emphasize:

> The results are concerning because they include fat mass and waist circumference, which are associated with the metabolic syndrome (Straker et al., 2005) in adults treated with antipsychotic medications and heart disease in the general population (de Michele et al., 2002). Moreover, abnormal childhood weight and metabolic status adversely affect adult cardiovascular outcomes (Srinivasan et al., 2002; Sinaiko et al., 1999; Bhargava et al., 2004; Baker et al., 2007) via continuation of these risk factors (Juonala et al., 2006) or independent or accelerated mechanisms." (Raitakari et al., 2003). (Correll et al., 2009, p. 1768)

This means that even after a normalization of weight, the risk of later cardiovascular disorders can remain elevated. Correll himself made the following comment in an interview: *"*Everyone should think twice before actually prescribing these medications.*"* An editorial in JAMA (Journal of the American Medical Association) offered the following formulation: *"*These results challenge the widespread use of atypical antipsychotic medications in youth" (Varley & McCellan, 2009, p. 1811).

The development of metabolic side effects in children and adolescents over one year was investigated in a retrospective cohort study of 28,868 patients enrolled in the Tennessee Medicaid Programs during or after neuroleptic treatment (Bobo et al., 2013). Compared to a control group, there was a 3.3-fold increase of new-onset Type-II diabetes, depending on the cumulative total dosage of neuroleptics. The ingestion of more than 100 mg CPZ-equivalents (equal to about 5 mg haloperidol/day over one year) caused a 5.4-fold increase in risk.

The risk of diabetes remained high (2.57 times above normal) during the first year after discontinuation of neuroleptics, and was associated with all antipsychotics of the second generation (87% of subjects), including risperidone and aripiprazole. Here, however, selection effects can play a role in prescribing practices. This increased risk was also noted under neuroleptic treatment for non-psychotic conditions, and therefore cannot be considered specific to these disorders.

But what are well-controlled studies saying about the use of these substances in everyday clinical practice? Are discontinuation rates similarly high, or unacceptably or even irresponsibly low? And are parents advocating for treatment with neuroleptics due to a lack of information, and in spite of unacceptably damaging side effects? Finally, might already irreversible damage and higher relapse rates due to sudden withdrawal lead to poorer outcomes than if the person had never been placed on a neuroleptic in the first place?

The fact is that in the USA, neuroleptics are being prescribed primarily for non-psychotic disorders: ADHD, PTSD, aggressive behavior, and so-called bipolar disorders, often diagnosed at an early age. Girls experience more pronounced side effects than boys: weight gain, type II diabetes, dyslipidemias, urogenital and gastrointestinal disturbances, and neurological symptoms (Jerrell et al., 2008).

The lucrative market for neuroleptics seems to be headed towards further expansion. Antipsychotics have continued to grow with $18.2 billion in sales in the US in 2011, up $2.1 billion over 2010, with more than 57 million prescriptions in 2011 in the US. Three drugs—Abilify ($5.2 billion sales), Seroquel ($4.6 billion sales), and Zyprexa ($3 billion sales)—account for >65% of the total $18.2 billion spent on antipsychotics in 2011 in the US. Zyprexa lost patent protection in October 2011, Seroquel followed in 2012, and Abilify falls to generic competition outside the United States in 2014 and within the United States in 2015 (Lindsley, 2012). Most atypical antipsychotics will lose patent exclusivity, resulting in a compound annual growth rate (CAGR) of -3.7%. The worldwide market is expected to decrease from 18 to 14.5 billion US$ in 2014. Nevertheless, antipsychotic drug sales are expected to remain strong in long-acting injectable (depot) formulations, which are forecast to record a 16.6% compound annual growth rate (CAGR) during this time period, increasing from $1.5 billion in 2009 to $3.2 billion in 2014 (BBC research, 2010).

Children and adolescents are being targeted as the population with the greatest potential for market growth. This trend seems unabated, and has suffered relatively minor disturbances due to unscrupulous off-label marketing. But ultimately, these prescriptions are written by medical specialists. There are no regulatory mechanisms. Liability lawsuits are rarely brought and have little chance of success. Expert witnesses tend to protect the professionals rather than the consumers. Children and adolescents are the victims.

7. Discontinuation of neuroleptics

7.1 Supported tapering and discontinuation attempts

A recent and widely noted study by Wunderink at al. (2013) demonstrates the effects of gradual tapering and discontinuation in a randomized controlled field study. Initially the study was designed as a 2-year prospective randomized controlled trial (Wunderink et al., 2007) and started in 2001 with 128 included patients with a first episode of first-episode

of schizophrenia or a related psychotic disorder who had shown initial and sustained clinical improvement of positive symptoms to remission over at least 6 months and had largely returned to full functionality (88% of enrollees). This group was described as the best half of the total sample by the authors. After the initial 6 months of positive symptom improvement, 103 of these patients were randomized into two different treatment strategies: They received either an antipsychotic maintenance therapy or the antipsychotics were gradually tapered off during the follow up period of 18 months and restarted or retapered when early warning sings or positive symptoms reappeared. This has been described as a "more conservative treatment strategy in patients assigned to the discontinuation condition. Clinicians might have been very keen on the prodromal symptoms in these patients, being aware of the risk of relapse, while tapering the dose or discontinuing antipsychotics. " (Wunderink et al 2007, p. 659) "Prodromal symptoms" prompted an immediate increase of the dosage, suggesting that this early response to potential withdrawal symptoms might have made it more difficult to further reduce doses. In the experimental arm 50% were taken off neuroleptics during this follow up period and 30% restarted neuroleptics.

The outpatient or community care as well as visits to psychiatrists, community psychiatric nurses, or crisis intervention contacts were similar in both groups. No further psychotherapy (family or individual) was provided. Therefore, it is quite likely that the observed differences in course and outcome were related to different neuroleptic dosages. After 2 years the results were somehow disappointing: "Twice as many relapses occurred with the discontinuation strategy (43% vs. 21%). Of patients who received the strategy, approximately 20% were successfully discontinued. Recurrent symptoms caused another approximately 30% to restart antipsychotic treatment, while in the remaining 50% of the patients discontinuation was not feasible at all. There were no advantages of the discontinuation strategy regarding functional outcome. " (Wunderink et al 2007, p. 654).
At the end of this trial, all patients consented to a follow-up and 5 years later (i.e. 7 years in total) the research assistants from the original study contacted them for a one-time interview regarding the course and outcome of psychosis during the follow-up period. One hundred three (80,5%) from the inital 128 participants consented to take part. 18

patients refused further participation, 1 patient had committed suicide, and 6 individuals were lost to follow-up.

In the follow-up investigation, the following parameters were recorded: symptom severity (PANSS) and social functioning level (GSDS scale) during the past six months, the type and dose of antipsychotic medication during the last two years and all relapses throughout the seven-year period. A symptomatic relapse was defined as an exacerbation of symptoms during at least 1 week with at least 1 PANSS positive symtom score above 3 (mild).

These were the results: Overall, the average number of psychotic relapses was 1.24 for the entire period. They did not differ significantly in the two treatment arms: dose reduction/discontinuation (DR) 1.13 vs. maintenance therapy (MT) 1.35. Although the patients in the DR group in the first two years had twice as many relapses as the patients who received MT, however, after about three years, the difference in relapse rates was no longer significant, and it remained that way by the end of seven years.

It took about 3 years for the comparably better course and outcome in the dose reduction/discontinuation arm to set in. After seven years 30 patients of the total sample (29%) had reached a recovery, but more patients which had been treated in the initial DR arm with 21 patients (40.4%) compared to only 9 patients (17.6%) in the MT arm. Patients in the DR arm, at a trend level ($p = 0.07$), were more frequently engaged in an activity of at least 16 hours/week.

Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Characteristic	No. (%)		
	DR (n = 52)	MT (n = 51)	Total Sample (n = 103)
Recovery	21 (40.4)	9 (17.6)	30 (29.1)
Remission			
Symptomatic	36 (69.2)	34 (66.7)	70 (68.0)
Functional	24 (46.2)	10 (19.6)	34 (33.0)

Table 8: Recovery-rates with supported dose-reduction (DR) and continuous maintenance dose treatment (MT) (from: Wunderink et al., 2007, p. 916)

Status of symptomatic remission was not different in the two arms. However, significantly ($p = 0.01$) more patients achieved a functional remission with the DR strategy. Twenty-eight percent of patients achieved neither symptomatic nor functional remission.

During the follow up period no further specific dose reduction protocol or program was installed. 17 patients successfully discontinued antipsychotic treatment in the original trial. At the 7-year follow-up, an additional 3 in the DR group and 3 MT arm had stopped taking antipsychotics during the last 2 years amounting to a total of 17 patients who had stopped antipsychotic therapy at follow-up: 11 (21%) of the DR group and 6 patients (12%) of the MT group.

In the 34 successfully discontinued/dose reduction patients, symptomatic remission was achieved by 85.3% and functional remission by 55.9% of the patients, and with a mean number of 0.71 relapses during the 7-year follow-up. Compared with the 69 not discontinued/tapered patients from both arms of the trial, symptomatic remission happened in 59.4% and functional remission in 21.7% of them, and with a mean number of 1.51 relapses during the 7-year follow-up. All these differences were significant.

In a stepwise logistic regression analysis of predictors of successful discontinuation or dose reduction to a mean daily dose of less than 1mg of haloperidol equivalents during

the last 2 years of follow up only successful discontinuation of antipsychotics during the original trial predicited this significantly and independently. The other tested predictors (a) no relapse occurring during follow-up (b) short duration of untreated psychosis (c) better social functioning (d) less severe PANSS general symptoms did not survive this analysis.

Dose-reductions were begun 6 months after remission and after 7 years, the average dosage was at 2.8 mg in the dose reduction arm versus 4.1 mg haloperidol equivalents for the maintenance group, both groups essentially quite low. Another 21% of participants, at the end of year 7, were taking dosages below 1 mg haloperidol-equivalents. This would amount to 22 patients (42%) in the DR group without substantial antipsychotic medication (p. 918).

This study showed that early and continuously supported dose-reduction and—whenever possible—discontinuation leads to a nearly doubled rate of recovery (day-to-day functioning) of 40.4%, along with a similar remission rate in symptomatology between experimental and control groups (68%). If a more sophisticated and ongoing tapering strategy would have been used, taking withdrawal symptoms into consideration and if other forms of psychotherapy would have been included, the outcome might have been even better.

Also, the other not-included half of the sample, those with less good prognosis, could not be expected to have experienced more advantage from neuroleptics than those included in the study. In this group the response rate to neuroleptics is mostly below 30% PANSS reduction, which is only a minimal or even less clinical improvement (see Levine et al 2010). In the course of long term treatment, worsening of symptoms under neuroleptics has to be expected (see Levine et al 2012).

This demonstrates that attempts at discontinuing or lowering neuroleptics by even small amounts could be very significant, even if this does not result in a change of symptomatology. The advantages of lower dosages become apparent when the capacity

for self-care, activities of daily living, familial and marital relations, friendships, community integration and employment are taken into consideration. The authors also affirm that the patient has to become the key person in his/her own treatment, while the doctor provides support in arriving at a well-founded decision about antipsychotic treatment.

7.2 Studies concerning the withdrawal of neuroleptics after the first psychotic episode

There are currently 8 studies where neuroleptics were discontinued within 4-6 weeks after a first psychotic episode. In one study, this occurred after "6-12 weeks" (Boonstra et al., 2011). A review of these studies by Emsley et al. (2012a) found that around 80% of the subjects experienced a relapse within one year. Many of these patients showed initial psychotic symptoms within several days or weeks after the discontinuation (Emsley et al., 2013a).

Table 4. Studies of Intermittent Treatment After a First Episode of Psychosis

Study	N	Treatment Duration	Symptom Recurrence Rate, %				Comparator Recurrence Rate, %
			12 Months	18 Months	24 Months	36 Months	
Kane et al (1982)[14]	28	Not specified	41				0
Crow et al (1986)[15]	120	Not specified			62		46
Gitlin et al (2001)[16]	53	3 months in remission	78		96		NA
Wunderink et al (2007)[17]	131	6 months in remission		43			21
Gaebel et al (2010)[18]	44	12 months	57				4
Chen et al (2010)[19]	178	12 months+	79				41
Emsley et al (current study)	33	24 months	79		94	97	NA

Abbreviation: NA = not applicable.

Table 9: Studies of antipsychotic discontinuation after first psychotic episode (from Emsley et al., 2012a, p. e545)

These symptoms at relapse appear to intensify much quicker than during the first psychotic episode (Emsley et al., 2012a). Frequently, the positive symptoms used as an indication of relapse were not assessed using standardized instruments, but in most studies were defined by using a lower threshold to justify an earlier pharmacological intervention, thus making a distinction between withdrawal syndrome and psychotic relapse more difficult. There is no sure-fire method to distinguish between an *actual*

relapse, psychotic withdrawal phenomena, or supersensitivity psychosis. In general, withdrawal symptoms tend to occur rapidly, within days or few weeks. For such symptoms, a rather quick reinstatement of the most recent neuroleptic dose seems to be the rule. None of these studies provided a specific preparation or support to help participants deal with early symptoms. According to Wunderink et al. (2007, 2013), whenever gradual steps of dose-reduction and retapering (return to the previous dosage of medication) were employed, such symptoms rarely lasted longer than four weeks and hospitalization was an exception (10%).

In one of the studies cited by Emsley et al. (2012a), relapse was standardized and defined with a higher threshold of symptoms (25% increase in PANSS total score) before the medication was started. The average length of time preceding a response to a neuroleptic once drug treatment was reintroduced was 12 weeks, and hospitalizations occurred in 38% of the subjects. In comparison to the first episode, this phase of remission took 3 weeks longer under renewed medication (Emsley et al., 2013b). This is similar to the findings of an earlier study by Lieberman et al. (1996).

In all 8 studies of neuroleptic withdrawal, patients returned to the symptom level they had exhibited at the end of the first episode, and their day-to-day functioning did not deteriorate (Curson et al., 1986; Kane et al., 1986; Wunderink et al., 2007; Glovinsky et al., 1992; Gilbert et al., 1995; Gitlin et al., 2001; Wunderink et al., 2013). Sometimes symptoms even improved slightly (Emsley et al., 2012a) and functionality rose markedly, due to the dose-reduction that had been achieved (Wunderink et al., 2013). Even people with "treatment-refractory schizophrenia" who participated in a six-week placebo study experienced symptom reduction to the levels of the earlier remission (Wyatt et al., 1999). On the other hand, 14% of individuals who had experienced several prior episodes of psychosis did not achieve post-relapse remission until one year after termination of the study (Emsley et al., 2012b). However, 18% of the subjects who were taking neuroleptics continuously also experienced a relapse within one year, which could be considered a supersensitivity psychosis. It should also be taken into consideration that the relapse rate following withdrawal after a prolonged period of neuroleptic treatment is certainly not

lower; if anything, this might be increased after such long-term treatment (Emsley et al., 2013a).

In their meta-analysis, Leucht et al. (2012) noticed a difference in relapse rates over one year between patients treated with neuroleptics versus placebo (27% vs. 64%). Ten percent of patients given drugs were readmitted compared with 25% given placebo. The duration of neuroleptic withdrawal did not seem to influence the relapse rate. Such withdrawal generally took a maximum of 4 weeks when tapering tablets or simply discontinuing a depot medication. These studies used so-called inert placebos that had no effects of their own, meaning that participants could easily be identified as members of one or the other study group. Placebo effects are certainly not negligible in the treatment of individuals diagnosed with "schizophrenia" (Kinon et al., 2011).

Studies on individuals experiencing a first episode of psychosis (FEP) (see Tab. 10) show a 21% rate of successful discontinuation attempts. Another study reported a rate of 25% for fully remitted patients (Nishikawa et al., 2007). A meta-analysis of 1006 patients revealed recovery rates of 40% (Viguera et al., 1997) after abrupt withdrawal of oral maintenance neuroleptic treatment.

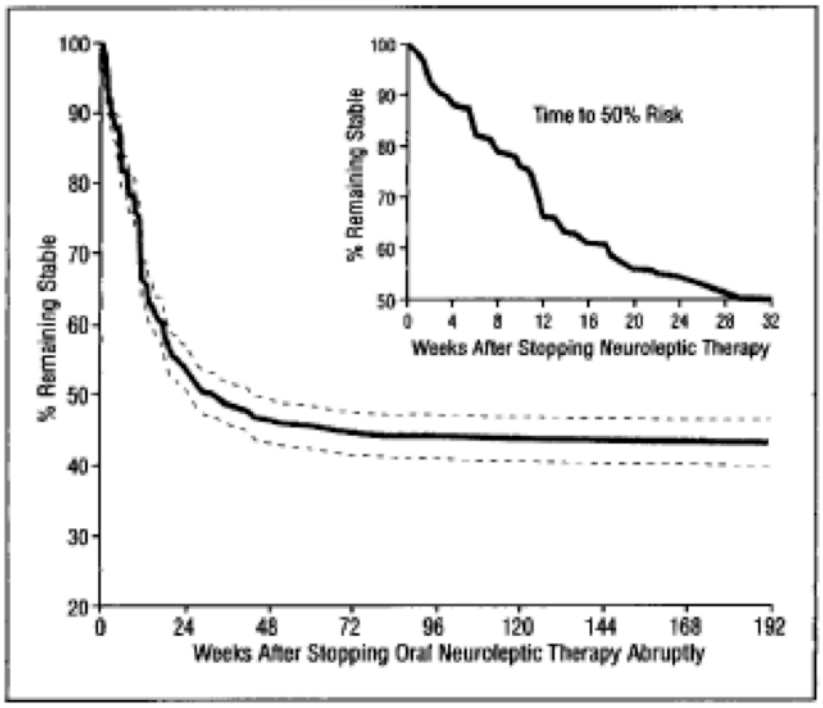

Fig. 11: Relapse rates from studies that abruptly discontinued oral maintenance neuroleptic treatment in patients with schizophrenia. Data are the percentage of patients who remained stable vs. the weeks after the abrupt stopping of treatment (n=1006). Dashed lines indicate 95% confidence intervals. The inset shows the time to a 50% relapse rate (7.5 months.) (From Viguera et al., 1997, p. 52)

In a further meta-analysis of discontinuation studies, researchers identified differential relapse rates for outpatients and inpatients. Researchers found that among 211 outpatients, the proportion of continuously stable patients following abrupt drug discontinuation rose to 60% over 4 years, and that few relapses occurred after withdrawn patients reached the six-month mark without relapsing.

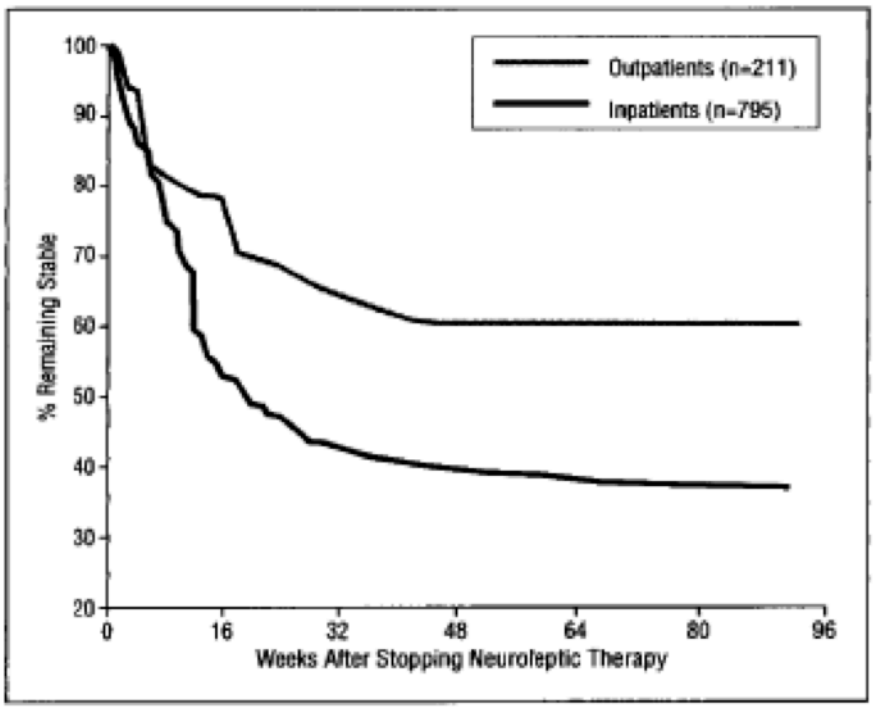

Fig. 12: Relapse rates comparing inpatients and outpatients after abrupt discontinuation of oral neuroleptic treatment (from Viguera et al., 1997, p. 52)

In a later analysis, Boshes et al. (2002) discovered that most patients who did not relapse remained clinically stable beyond 4 years, and no longer took any neuroleptics. In their review, Gilbert et al. (1995) found a relapse rate of 16% within one year under neuroleptic maintenance treatment, and 50% after discontinuation. Frequently, four or more attempts are necessary and reasonable in order to successfully discontinue neuroleptics (Nishikawa et al., 2007). Even when including subjects with multiple episodes, the existing discontinuation studies have demonstrated that up to 60% of cases can withdraw successfully (Viguera et al., 1997; Baldessarini et al., 1995).

Even under neuroleptic maintenance treatment, 3.5% of individuals with a history of multiple episodes per month experience a relapse, primarily due to a loss of effectiveness, and 11% per month experience a relapse due to taking themselves off the medication ("non-compliance"), according to a review of the U.S. literature (Weiden et al., 1995). The rate of unilateral discontinuation in U.S. community mental health clinics was

calculated at 7% per month. The share of inpatient costs due to loss of effectiveness of neuroleptics was estimated at 60%, 40% of which was estimated to be due to "non-adherence" (Weiden et al., 1995).

8. Recovery Issues

8.1 Predictors of recovery

Álvarez-Jiménez et al. (2012) investigated the question of to what extent treatment-related predictors might be relevant for long-term psychosocial recovery, by using selected data from an epidemiologically representative 7.5 year follow-up study of EPPIC, an early detection project in Melbourne, Australia. Two hundred nine individuals in a first episode of psychosis were treated initially and re-examined after 8 and 14 months, and again after 7.5 years. Treatment through the EPPIC project lasted only 18 months, at which point people were transitioned into the established service system. After 7.5 years, 26% of patients (N=54) had experienced full functional recovery. The following predictor variables were considered: duration of untreated psychosis (DUP); time until treatment response for positive symptoms; length of inpatient stay; level of social and occupational functioning; social isolation prior to onset of illness; social withdrawal after enrollment in the project; degree of insight. Only the following predictors were related to full functional recovery: A DUP of less than 4 weeks was a predictor of symptomatic remission after 8 months (Odds Ratio = 3.25) and milder symptoms according to the BPRS and SANS, but not predictive of symptomatology or functional recovery at a later point, beginning at 14 months. A DUP longer than 4 weeks was not predictive of symptom reduction or greater functional recovery.[1]

Neither group (with and without functional recovery after 7.5 years) showed a significant difference in the remission of positive symptoms at onset, after 8 weeks (83%) and 8

[1] An odds ratio (OR) represents one way to quantify how strong the presence or absence of property A is associated with the presence or absence of property B in a given population. An odds ratio of 1 means there is no different. An OR of 3.25 indicates a 3.25 times greater chance/risk for an event in comparison to the risk in the control group.

months (80%). A remission of positive symptoms at any of the follow-up points was also not a significant predictor of functional recovery after 7.5 years.

A remission of negative symptoms after 8 months alone (OR=3.2) or in conjunction with a remission of positive symptoms (OR=4.45) was a predictor of functional recovery after 14 months. Negative symptoms are hardly favorably impacted by neuroleptics, but on the other hand, neuroleptics can cause negative symptoms in a dose-related fashion. Functional recovery after 14 months was the strongest (OR = 6.7; explaining 20% of the variance) and ultimately the only predictor for functional recovery after 7.5 years. A symptomatic remission in combination with functional recovery after 14 months was no better a predictor than functional recovery alone. Several other predictors did not turn out to be significant.

A remission of negative symptoms after 14 months was *not* a predictor for remission of the same or for functional recovery after 7.5 years. However, functional recovery after 14 months was a significant predictor for the remission of negative symptoms or a functional recovery after 7.5 years (OR = 2.6). In addition, 67% of patients with functional recovery had already been off neuroleptics after 14 months, and 61% still were without them during the last two years of the study. These are the only time frames that were evaluated in this study. The proportion of subjects off neuroleptics after 14 months (OR = 7.7) and during the last two years of the study (OR = 7.8) was the best predictor of functional recovery after 7.5 years (Álvarez-Jiménez et al, 2012, table 2, p. 602). Nevertheless, this variable was not evaluated as a predictor and only briefly mentioned as a comment on the last page. Remarkably, only 41% of individuals with functional recovery were deemed to have a high level of insight.

The fact that a remission of positive symptoms has no or very little influence on functional recovery after 7.5 years is a very important finding, since the former is a central hypothesis and goal of neuroleptic treatment. According to the authors, these results confirm that early functional and occupational recovery rather than symptomatic remission is the key factor in the prevention of chronic negative symptoms and

occupational disability. The authors discuss possible effects—including neurobiological—of intimate relationships, a meaningful life, positive outlook towards the future, positive emotions that curtail vulnerability to stress, and social support, postulating a "positive spiral" towards wellbeing that functions as a buffer against potentially harmful emotional reactions to stressful life events. The results of this study are sobering when it comes to the effects of pharmacotherapy and early detection. Freedom from neuroleptics, low dosages (considering the results of Wunderink's study), and early vocational and educational integration seem to have a much stronger effect.

8.2 Early intervention of psychoses

To this day, early intervention projects have not focused decisively enough on vocational integration as well as tapering or discontinuation of neuroleptics. This study also puts the biological-reductionist construct of negative symptoms into question. The findings indicate that emotional, motivational and relational aspects are far more important, and the influence of living conditions on course and outcome much greater, than is usually assumed.

Even creative art therapies show a large effect on negative symptoms even 6 months after the end of the treatment (NICE, 2009). Lowest possible dosages show the best pharmacologic effects. Early intervention with neuroleptics in so-called "ultra-high-risk syndrome" patients does not seem to be indicated at all, according to current science. Better results are available from the use of omega-3-fatty acids (Fusar-Poli et al., 2013a).

Early detection projects that reduce DUP to less than 28 days might have primarily treated patients with brief psychoses, and as a result achieved better outcomes (Warner, 2005). Such patients would have been excluded from a study of "schizophrenia"-spectrum disorders. These patients are treated early with neuroleptics, even though they might be suffering from a brief, remitting psychosis that would have passed without neuroleptics.

At the same time, it is becoming increasingly apparent that maximally achievable freedom from neuroleptics seems to be the best predictor for a course with the greatest potential for recovery. The usual early intervention projects do not appear to employ an algorithm for earliest possible dose-reduction and discontinuation attempts, which tends to be key. Furthermore, there still is the notion that neuroleptic maintenance treatment improves long-term outcome. Symptom remission seems less decisive than maximally supportive and encouraging follow-up aimed at a life where social and occupational integration occurs as early as possible, along with maximal freedom from neuroleptics.

8.3 Initial acute treatment without neuroleptics.

Initial treatment in acute episodes without neuroleptics, or with a delayed or selective use of neuroleptics, is the approach that enables the largest number of patients to be treated successfully without these drugs. Due to the rapid transformation of receptors and other brain structures under neuroleptics, selective use during initial episodes is likely to result in the greatest proportion of patients who can remain free of these medications.

Study	Diagnostic Sytem	% Without Neuroleptics	Initial Time Without Neuroleptics	Method	Effect Size	Length of Study
St. Agnews (Rappaport, 1978)	DSM II	61%	4-6 weeks	RCT	0.18	3 years
Soteria California (Bola & Mosher, 2003)	DSM II	43%	4-6 weeks	1st cohort; quasi-experimental	0.19	2 years
Soteria Bern (Ciompi, 1992)	DSM III-R	27%	3-4 weeks	Case-control study Matched pairs	0.09	2 years
API Project (Lehtinen, 2000)	DSM III-R	43%	3 weeks	Quasi-experimental All FEPs from six regions	0.16	2 years
NIPS Project (Alanen 1994, 1997, 2009)	DSM III-R	56% after five years	2-3 weeks	Prospective cohort study	n/a	5 years
Open Dialogue (Seikkula, 2003, 2006)	DSM III-R	60%	3 weeks	Cohort study, all FEPs from 1 region	Significantly better w/o neuroleptics	5 years
Parachute Project (Cullberg 2002, 2006)	DSM IV	42%	1-2 weeks	Quasi-experimental Multi-center 17 sites; 1 control site	n/a	2 years
Chicago 15-year Followup (Harrow 2007)	DSM III R	40%	Initially with neuroleptics; discontinuation later	Case-control study	Significantly better w/o neuroleptics	15 years
Cochrane metanalysis (Thornley 2000)	Diverse	Almost 40%	RCT, neuroleptics vs. placebo	Metanalysis of RCTs, unspecified miles	n/a	Variable

Table 10. Overview of studies concerning acute treatment without neuroleptics for first-episode psychosis (FEP.) Explanation of the values used in the table: Effect size indicates the relative effect, where 0.1 is a small effect, 0.3 is a moderate effect, and 0.5 a strong effect.

The fact that approximately 40% of patients with an FEP that falls within the "schizophrenia" spectrum can be treated without neuroleptics at onset and over prolonged periods of time has been proven by the use of special residential settings that function as alternatives to the hospital, e.g. "Soteria**"** (Bola & Mosher, 2002), as well as dedicated teams that provide acute treatment within the clients' real-life environment (Need-Adapted Treatment) (Alanen, 2001; Aderhold et al., 2003).

Patients who could be treated without neuroleptics did better if they were never put on these medications in the first place (Lehtinen et al., 2000). Bola et al's review (2009) of the five existing randomized and quasi-experimental studies on this question demonstrated an overall effect-size of r = 0.17, favoring the experimental groups within the first two years, when compared to the controls. We also know from the longitudinal

studies by Harrow et al. (2014) and Wunderink et al. (2013) that strong positive effects can be sustained beyond years 2 and 3. The results from a region in Finland where the systemic Open Dialogue method was developed, and where the greatest experience with this method was gathered over a period of 20 years, also need to be taken into consideration. This work showed that 70% of the patients with a first episode of non-affective psychosis could be treated without neuroleptics, and that 76% managed to establish themselves in a vocational or educational setting following such treatment (Seikkula et al., 2006; Seikkula et al., 2011). This study also included patients with briefer psychotic episodes. Quite possibly, many of these brief psychotic episodes treated with early intervention but without neuroleptics might have otherwise developed into an ongoing "schizophrenia."

Another randomized study demonstrated that delaying neuroleptics by 4 weeks does not result in poorer outcome after 2 years (Johnstone et al., 1999). In these situations, early intervention does not mean beginning treatment with neuroleptics as early as possible, but rather introducing a complex psychosocial and psychotherapeutic treatment method. These two approaches complement each other very well. The early intervention approach of Need Adapted Treatment appears to be quite well suited to reaching individuals after only a short period of psychotic symptoms, and thereby preventing a transition from such brief episodes to an ongoing condition termed "schizophrenia" (Seikkula et al., 2011).

More than half of the patients who were later diagnosed with "schizophrenia" (41% vs. 22% in the cohorts from 1997 and 2005, respectively) could be treated entirely without neuroleptics (Seikkula, personal communication - unpublished data). Curiously, the Soteria approach showed its greatest effects among individuals with a gradual onset and a "schizophrenia" diagnosis; these people achieved an 80% better overall result and had a 40% chance of entering the workforce in comparison with the control group (Bola & Mosher, 2002). No specific ongoing outpatient treatment was offered as part of the Soteria model. However, mutual support among former Soteria residents and staff was promoted.

Unlike Soteria, more than 50% of clients enrolled in Need Adapted Treatment also participated in individual psychotherapy according to their own preference (Seikkula, 2011). Need Adapted Treatment is conceived according to a systemic psychodynamic paradigm, which does not rule out additional therapies such as cognitive behavioral work in certain regions of Finland. Cooperation with the patient's family and network is another key element of the Need Adapted Treatment model, which often also means including the individual psychotherapists in network meetings.

Combining these two approaches, Soteria and Need Adapted Treatment, with the following key structural elements might be an especially advantageous treatment option for psychosis:

- Systemic, team-based early intervention within the actual living environment of the clients ("in vivo") that involves their families and social network in the therapeutic process from the beginning.

- Continuous support by these teams over several years, or as long as necessary (relational continuity).

- Integration of experts-by-experience (peer workers) into these teams.

- Whenever necessary, a small, trauma-sensitive residential setting ("crisis respite") should be available, with non-professionals and peer workers as an especially effective part of the staff.

- Individual psychotherapy should be offered, as long as it makes sense to the client. The particular therapeutic method might vary, and might include trauma-informed elements. A strong collaboration of the individual therapist with the community-based team is very important, but must be weighed against confidentiality requirements.

- Creative psychotherapies, such as art, music or dance therapy. Supported Employment Teams (separately or as part of the crisis-team) that aim at the earliest possible (re)integration into training institutions or employment in the open market.

Dedicated community-based teams, systemic interventions with the family, and individual psychotherapy have each been evaluated separately, and are all recommended by the U.K. NICE-guidelines (2009) as core interventions. According to the available research, family interventions appear to have the most favorable effects on relapse prevention (Pharoah et al., 2006; Garety, 2003).

9. What To Do?

9.1 General principles

Basically, it has to be recognized that neuroleptics are only one element in a treatment environment that needs to be as flexible as possible, as well as subjectively oriented and relationally continuous. In such a context, the following are things that should be considered when it comes to the use of neuroleptics:

- There is considerable heterogeneity among individuals diagnosed with "schizophrenia," and even more so within the entire spectrum of psychotic disorders.

- Neuroleptics also have individually heterogeneous effects, which remain unpredictable to this day. For only a small portion of the users, neuroleptics have a sustained and clinically relevant "antipsychotic" effect (NNT=6) (Leucht et al., 2009).

- Studies usually offer conclusions about an entire group of highly selected subjects. Most of the results are therefore not applicable to the majority of patients/users (low external validity and "effectiveness"). Therefore, scientific "evidence" is frequently lacking and unhelpful to the decision-making process (Leucht et al., 2006b).

- Neuroleptics are not curative. Besides their somatic and hormonal side effects, neurotoxic effects are becoming increasingly obvious. Therefore, the usual logic of "more is better" does not apply; it rather seems to be a case of "less is more." (Samaha et al., 2008).

- Due to the fact that the harmfulness of neuroleptics is usually dose-dependent, many researchers have begun to recommend only the lowest possible dose in order to manage symptoms. In many cases, a full remission of symptoms cannot be achieved in the course of treatment (Ho et al., 2012; Kapur et al., 2006).

- The longer that neuroleptics are taken, the more severe their neurotoxic side effects, which makes symptom reduction even less likely (Remington et al., 2010).

- A blockade of D2 receptors cannot resolve the traumatic and overwhelming experiences and emotions that occurred before the psychotic crisis.

- The biologization and medicalization of psychosis and its treatment have aggravated self-stigma and negative attitudes towards individuals with these experiences, resulting in social exclusion (Angermeyer et al., 2013).
- Only an integration of the following elements into the treatment and support system will increase the chances for a successful and

meaningful life: emotional, familial and relational elements; spirituality and religion; social and vocational aspirations; addressing problematic biographical experiences; and the development and promotion of multiple resources and capabilities.

What are the consequences [implications] of what has been said so far?

9.2 Acute treatment with neuroleptics

The lowest necessary dose of neuroleptics can only be determined by using an initial dose at the lowest limit of the dose range, increasing it gradually over several weeks, and only in the case of insufficient clinical effects. This was already discussed in detail on page 79-83.

9.3 Ongoing monitoring

Whoever prescribes potentially damaging medications needs to ascertain whether such damage is actually occurring, and provide this information to the patient. The most salient tests for monitoring these effects are summarized in Table 8:

Parameter to be monitored	Onset of Rx	6 Weeks	3 Months	1 Year
Smoking, physical activity, nutrition	Yes	Yes	Yes	Yes
Weight/BMI	Yes	Yes	Yes	Yes
Abdominal circumference	Yes	Yes	Yes	Yes
Blood pressure	Yes	Yes	Yes	Yes
Fasting blood sugar	Yes	Yes	Yes	Yes
Fasting blood lipids	Yes		Yes	Yes
EKG	Yes	Yes, or as per cardiology		Yes
Prolactin levels	Yes		Yes in case of sexual dysfunction	Yes
Dental status	Yes			Yes

Table 11. Necessary parameters to be monitored under neuroleptic treatment (from: de Hert et al., 2011b, p. 142)

9.4 Responding to a patient's wish to discontinue

Considering the 50% median rate of spontaneous discontinuation within one year (Cramer et al., 1998) and 75% within two years (Velligan et al., 2009), researchers such as Wunderink et al. (2013), Emsley et al. (2013), and McGorry et al. (2013) recommend that the wish to come off neuroleptics should be taken seriously. Patients should be informed about the higher risk of relapse, followed by close cooperation in helping the patient make a careful and well-supported attempt to reduce and discontinue the medication. This is also suggested in certain treatment guidelines (NICE 2009, p. 21).

From this perspective, the issue is not to avoid relapses per se, but to support people through eventual relapses as well as possible, in order to limit their duration and severity. Such relapses are easier to deal with than full-blown decompensations without support.

In addition, this approach makes it more likely to identify the lowest possible dose, which is proven to be associated with lower toxicity and better functional recovery. However, such an approach has not been accepted by many practitioners.

This procedure would also contradict the old guidelines for "schizophrenia" promulgated by the German Association for Psychiatry, Psychotherapy and Psychosomatics from 2005, where it is stated: "Following a first relapse, antipsychotic medication should be continued for 2-5 years, and after multiple relapses most likely for life." U.S. guidelines spell out analogous treatment principles: "Minimizing risk of relapse in a remitted patient is a high priority, given the potential clinical, social, and vocational costs of relapse" (Lehmann et al., 2004*)*. Elsewhere, the US PORT guidelines from 2009 state:

> "The maintenance dosage for aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone should be the dose found to be effective for reducing positive psychotic symptoms in the acute phase of treatment. Since the last PORT review, no new evidence has emerged to warrant a change in the recommended dosage range or dosage reduction strategies during maintenance treatment with FGAs." (Buchanan et al., 2010, p. 77)

A recent systematic review of 14 available guidelines for treatment in the maintenance phase (Takeuchi et al., 2012) revealed that only 11 guidelines and algorithms referred to discontinuation of antipsychotics in maintenance treatment, and 10 of them did not recommend discontinuation of antipsychotics within five years; of these, only six recommended antipsychotic discontinuation for patients with first-episode psychosis. All nine guidelines and algorithms that referred to intermittent or targeted antipsychotic strategy contraindicated this strategy. In spite of the fact that the topic is being discussed widely, dose reduction or low-dose antipsychotic therapy in the maintenance phase is generally not recommended for SGAs, while it is sometimes acceptable for FGAs.

These guidelines should be adjusted to reflect the more recent research findings, rather than extending the influence of scientifically backward guidelines to clinical practice today. When professionals withdraw their support from someone who has expressed the desire to stop a medication, an unsupported, often abrupt discontinuation attempt is likely to follow. Such sudden withdrawals often lead to more severe psychoses, and a delay in reengagement with professional treatment in the absence of other support. As a result, the psychosis is extended for a period of several months, which could result in further shrinking of grey brain matter. This type of treatment failure should be considered the responsibility of the professionals rather than the patients, who are often blamed for discontinuing the medications.

In general, the dosages given in response to such situations tend to be excessive, especially when someone is being reintroduced to neuroleptics during a relapse. Patients who might have sound reasons to reduce neuroleptics rarely receive support from doctors and other mental health professionals. Doctors are considered even less supportive than non-medical psychotherapists, practitioners of complementary or alternative medicine, and self-help groups when it comes to an attempt to discontinue a neuroleptic (Read, 2005). In fact, several guidelines for withdrawal from neuroleptics written by former patients have been widely promulgated (Lehmann et al., 2013; Hall, 2012; Beyond meds website; Coming off drugs website).

9.5 Predictors of relapse and successful discontinuation

To this date, there are no sure predictors that might help anticipate the outcome of a withdrawal attempt. Some studies offer a few predictors for relapses (and unsuccessful withdrawal):

- Ongoing use of illicit substances (Alvarez-Jimenez et al., 2012)
- Critical comments and hostility from caregivers (Alvarez-Jimenez et al., 2012)
- Lower level of social functioning before the onset of psychotic symptoms (Alvarez-Jimenez et al., 2012)

- Premorbid schizoidal or schizotypal personality attributes (Chen et al., 2010)
- Difficult relationships between the consumer, his/her family, and mental health professionals (Csernansky et al., 2002).

The availability of social support is an important and protective factor for successful discontinuation (Norman et al., 2005). However, the relevant research base is rather thin. Psychiatrists appear to be no better than consumers in predicting the outcome of a discontinuation attempt (Read, 2005). Even if there are no definitive predictors (Johnstone et al., 1999), the following list of favorable circumstances gathered from various publications might shed some light on the matter:

- 6 months without symptoms (Falloon, 2006)
- 2 years without relapse (Lerner et al., 1995)
- low initial dose (van Kammen et al., 1996; Gitlin et al., 2001)
- brief episodes and hospitalizations (Marder et al., 1979)
- sudden onset of an acute psychosis (Vaillant et al., 1962; Schooler et al., 1967; Schooler et al., 1967; Goldstein et al., 1970; Silverman et al., 1975/76; Carpenter et al., 1977; Rappaport et al., 1978; Marder et al., 1979; Yung et al., 1980; Buckley et al., 1982; Fenton et al., 1987)
- good psychosocial functioning before onset of illness (Goldstein et al., 1970; Evans et al., 1972; Carpenter et al., 1977; Rappaport et al., 1978; Marder et al., 1979; Buckley, 1982; Fenton et al., 1987; Johnstone et al., 1990; Bola et al., 2002; Bola et al., 2006)
- later age of onset (Schooler et al., 1967; Marder et al., 1979; Gilbert et al., 1995; Bola et al., 2002)
- no psychiatric history among parents (Lehtinen et al., 2000)
- distinct triggers preceding episodes (Marder et al., 1979)
- internal attribution (Harrow et al., 2007)
- effective coping strategies (Falloon, 2006)

- capable of self-management during crises (Falloon, 2006)
- no current stressful life events
- low stress level in the social arena (Hogarty et al., 1991)
- low levels of Expressed Emotion (EE) among important network members (Hogarty et al., 1991)
- support from family and others (Marder et al., 1979; Norman et al., 2005)
- effective individual psychotherapy (Gottdiener et al., 2002)
- effective family therapy (Hogarty et al., 1991)

The following factors might be considered contraindications for a withdrawal attempt:

- dangerous risk-taking behavior during a past psychotic episode
- very sudden onset of severe psychotic symptoms
- increasing residual symptoms after relapse
- history of hard-to-treat relapses

9.6 Practical procedures for withdrawal and discontinuation attempts

It is advisable that such attempts should only take place with therapeutic support. A supportive social network is also very helpful. Service users should obtain as much information as possible before taking this step. Ideally, a network meeting (or several) encompassing all important professional and personal support staff should take place prior to the attempt, which includes the preparation of a crisis plan. Recognizing very early warning signs that might be more easily noticed by intimate partners or family members is crucial, along with developing an appropriate response. Personal risks, fears and options should be discussed with close network members and examined concerning their realistic validity. All available resources should be considered, and access to them arranged.

To keep withdrawal symptoms at a minimum, it might be advisable to proceed according to the 10% rule, according to which each step should involve a reduction by 10% or even less during the later stages of the process. Each reduction should occur at an interval of 4-6 weeks, and should only be repeated if a certain degree of stability has been achieved over a few weeks at this level. Survivors report that successful withdrawal often is accompanied by several months, even years, of experiencing residual symptoms and medication effects until stabilization sets in (Tranter & Healy 1998).

The longer a person has been on a certain medication, the slower he/she must proceed. When people have taken neuroleptics over 5 years, withdrawal should extend over two years or more. In the case of polypharmacy, only one drug at a time should be reduced, beginning with the one that might be given up most easily; that is, the substance with the least suspected effectiveness. The process should ideally begin during a period of relative emotional and social stability, unless a person is currently taking very high dosages or combinations of three or more neuroleptics. It is advisable to keep a brief diary/protocol detailing this process, possibly written by an associate. Healthy nutrition, fruit, lots of water, physical exercise, rest, and ample sleep beginning at 11 PM at the latest (possibly with the aid of valerian drops) are essential. Abstinence from alcohol, illicit drugs, and even caffeine is recommended.

Strong emotional reactions can be expected and will require support, possibly including creative expression or physical activity through sports and other types of exercise. Mental and physical withdrawal symptoms occur rapidly, and change over time. If they are too pronounced, the withdrawal is proceeding too quickly. At such a point, it would be good to return to the most recent or even slightly higher dose for a few days. Two to four weeks should pass before a next, even more careful withdrawal attempt. A period of mental stabilization needs to occur at every new dose level before the next reduction. Brief psychotic symptoms do not necessarily imply that the dose needs to be raised again. Stability can also be reached by other means. Here, a variety of psychosocial interventions might be of help, such as relaxation techniques, physical activities, following principles of recovery, coping techniques for hearing voices, individual

psychotherapy, family therapy, and traditional Chinese herbal medicine. Even a brief use of benzodiazepines might be helpful, especially for insomnia.

It also appears to be helpful when the person pursues another important life goal in addition to reducing the medication.

Frequent contacts (1-2 times/week) with trusted private or professional helpers might provide the necessary reassurance, should the person experience emotional instability. These supportive individuals could also provide additional assessments of the situation.

In some situations, only ongoing treatment at a lower dose rather than complete withdrawal can be achieved. Ongoing therapeutic support might make it possible to lower the dose even further in the future. Full withdrawal, even if well supported, is not always a necessary or reasonable last step. It should not be forced, and this decision should not be made at the beginning of the withdrawal process.

In this context, it is very important to assess withdrawal and discontinuation phenomena as accurately as possible. The following are possible withdrawal symptoms for neuroleptics (Breggin, 2013; Tranter et al., 1998; Lehmann et al., 2013):

- Psychotic symptoms that cannot be clearly distinguished from the original disturbance. They usually occur within days after reduction and tend to improve within 2-3 weeks.

- Emotional instability**,** anxiety, restlessness, depression, irritability, aggressively, and hypomanic symptoms. These occur within days or weeks following a reduction or discontinuation.

- Abnormal involuntary movements of face, lips, jaw, tongue, arms, wrists, hands, fingers, legs, knees, joints, toes, neck, shoulders, and hips. In some cases, i.e. when these are evidence for so-called

irreversible tardive dyskinesias, such symptoms might not go away and can cause severe agitation and anxiety.

The above-mentioned phenomena might persist for up to 1.5 years, according to Breggin. Furthermore, the following additional problems can occur:

- Cognitive problems, such as difficulties with concentration, attention and memory.

- Gastro-intestinal disturbances, nausea, vomiting, diarrhea, sweating, dizziness, tachycardia, high blood pressure, tremor, syncope, flu-like symptoms, sensitivity to pain, and headaches.

Symptoms in these areas can persist over weeks to months. Commonly, such symptoms remit almost fully within a few hours of resuming the most recent (higher) neuroleptic dose. The extent of symptoms is co-determined by the level of reduction. Therefore, it is even more important to proceed slowly and in small decrements.

To achieve a minimal dose or complete withdrawal from neuroleptics is particularly relevant for successful vocational rehabilitation, supported employment and community integration. Several studies have shown that the extent of occupational rehabilitation for individuals with psychosis is highest without neuroleptics (Carpenter et al., 1990, 1999; Herz et al., 1991; Johnstone et al., 1999; Seikkula et al., 2006; Seikkkula et al., 2011; Wunderink et al., 2007; Alvarez-Jiminez et al., 2012). This is one of the primary aims of social inclusion and the recovery movement. In our opinion, recovery and minimal/selective use of neuroleptics belong together.

9.7 Treating acute psychotic relapses with benzodiazepines

A recurrence of psychotic episodes after full remission can be treated successfully with benzodiazepines in 50% of cases (Carpenter et al., 1999). In this randomized, placebo-controlled doubIe-blind study, the experimental group immediately received 10 mg of

diazepam per day whenever they showed early symptoms, defined as a worsening of the BPRS score by 2 or more points. In the event of further deterioration, patients were started on neuroleptics. After successful stabilization under diazepam, the medication was gradually lowered over 4 weeks in two steps of 2 weeks each. The results for the group receiving benzodiazepines were slightly but not significantly better (Effect=0.21) than for the comparison group on neuroleptics, probably due to the small size of the sample (N=53). In other words, the patients on diazepam certainly did no worse than those on neuroleptics.

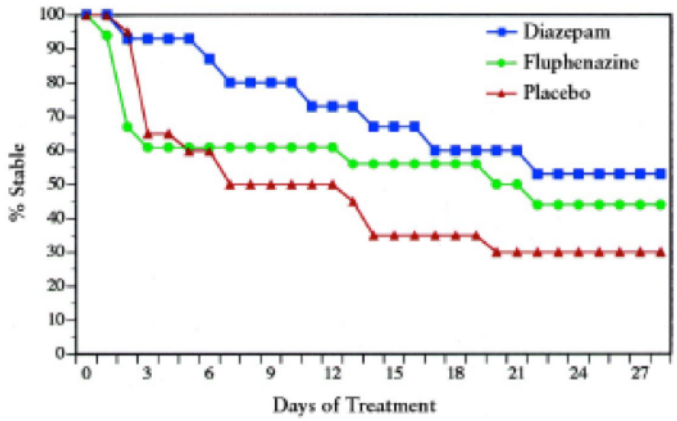

Figure 13: Percent of schizophrenia patients treated with diazepam (N= 15), fluphenazine (N=18) or placebo (N=20) whose symptoms did not progress.

In spite of the limited amount of studies comparing benzodiazepines to neuroleptics (4 over several weeks, and 2 over 1 year), a meta-analysis came to the conclusion that neuroleptics were not superior with regard to symptom remission and the relapse rate, based on an analysis of the pooled data (Volz et al., 2007; Dold et al., 2012). This suggests that benzodiazepines, not unlike neuroleptics, seem to be effective only for a subgroup of patients, and therefore might constitute an alternative treatment method for acute psychotic symptoms. This might be especially relevant for psychoses with an episodic course, thereby broadening the spectrum of treatment options. Whether acute psychoses should be considered neurotoxic in and of themselves, and thereby worsen outcome, seems increasingly dubious (McGlashan, 2006). For example, in a review of studies on neurocognition and morphological changes, Rund (2013) showed that most studies, especially methodologically better and larger ones, do not provide support for

this hypothesis. The most recent analysis of data from the Iowa study mentioned earlier concerning the loss of grey and white brain matter (Andreasen et al., 2013) finds only a correlation between such atrophy and prolonged relapses, but not the frequency of relapse.

9.8 The heterogeneous spectrum of neuroleptic use

Under the conditions elaborated earlier, there are 4 types of individuals diagnosed with "schizophrenia" who undergo an FEP:

1. Those who do not require any neuroleptics, self-limiting episode or episodes that respond favorably to psychosocial interventions (40%-possibly 60%).
2. Those with overall benefits from neuroleptics for symptom reduction (30%)
3. Those who need neuroleptics only briefly, episodic treatment on demand (10%)
4. Non-responders (15%-20%)

People with so called schizoaffective, delusional or acute transitory psychoses have a considerably greater chance of being treated without neuroleptics, according to exploratory studies (around 75%). In such situations, neuroleptics should only be used temporarily, if at all.

This results in a set of variable approaches for relapse prevention. Each approach seems best suited for a particular group of patients. Unfortunately, there have been hardly any studies to determine which form of psychotherapeutic or psychosocial treatment/support might best fit which kinds of clients. This issue is also rarely investigated in pharmacologic studies. Overall, we should be working with a continuum of medication strategies, ranging from no medication use at all to ongoing "maintenance" treatment. Whether complete discontinuation is possible cannot be determined for a particular individual, and it cannot be forced. The following medication strategies derive from existing studies. Which strategy seems optimal for particular individuals must be

determined by the delayed introduction of neuroleptics (3-6 weeks in Soteria and Need Adapted Treatment) or gradual dose-reduction. These are the options:

- no medication at all
- early use of benzodiazepines in crises only
- early use of neuroleptics in crises only – reaction to early warning signs
- very low dose of neuroleptics combined with benzodiazepines in crises
- very low dose of neuroleptics combined with higher doses in crises
- lower maintenance dose of neuroleptics
- higher maintenance dose of neuroleptics

9.9 Principle errors of psychiatric treatment-as-usual practices

In the following list, we summarize the most common mistakes made in psychiatric treatment for episodes of acute psychosis:

- FEP: Acute treatment without neuroleptics for 2-4 weeks is not offered
- Excessive initial dosages in acute situations
- Overly rapid dose increases
- Further increase of doses in case of a partial response
- Aggressive treatment of non-responders
- Polypharmaceutical combinations introduced early and sustained
- Combinations are rarely reversed
- Metabolic parameters are not monitored, leading to potentially preventable adverse results
- Limited mileu and psychotherapeutic competencies; psychotherapy is rarely offered

10. Psychotherapy and other non-drug treatments

10.1 Individual psychotherapy

The potential role of individual therapy for people diagnosed with "schizophrenia" remains an important question. The best results were achieved in cohort studies that evaluated a combination of network/family therapy and individual psychotherapy. Such a combination makes immediate sense. Usually, the resource-oriented work with families and access to a broader social network precedes individual therapy. Such treatment becomes useful in working through the psychotic experiences and other issues that may be too emotionally taxing at first, i.e. traumatic life experiences. Overall, psychotherapy is helpful for the development of individual autonomy (see above p. 81 for use of psychotherapy in Open Dialogue approach).

10.2 Cognitive therapy for individuals diagnosed with "schizophrenia" and persistent psychotic symptoms who are taking neuroleptics

Cognitive-behavioral therapy (CBT) shows a moderate effect when it comes to reducing psychotic and certain affective symptoms (Wykes et al., 2008). Another recently published meta-analysis that included 12 randomized studies also showed that CBT has fairly good results for this patient-group (Burns et al., 2014). For positive symptoms, they calculated an effect size of + 0.47 and for overall symptoms of + 0.52 (= moderate). These effects remained stable throughout the entire follow-up period. The dropout rate was fairly low (14%). These effects are larger than what might have been achieved through additional pharmacologic intervention. Consequently, the NICE guidelines for "schizophrenia" recommend the use of a minimum of 16 CBT sessions for patients with persistent positive symptoms while taking neuroleptics. Individual psychotherapy of any kind does not seem to have an impact on the hospitalization rate, according to available studies. However, there are several replicated studies that show such an effect for family therapy (Pilling et al., 2002), which suggests a benefit for combined treatments. Effects tied to specific CBT methods seem to be questionable.

Other appropriate forms of individual therapy, such as "supportive psychotherapy," show comparable effects. A meta-analysis of mostly non-randomized studies, involving psychodymamic psychotherapy adapted to specific disorders, shows only slightly lesser effects than CBT (Gottdiener & Haslam, 2002). A positive therapeutic relationship, i.e. a "good therapeutic fit," seems to be the most salient factor for its effectiveness rather than any specific psychotherapeutic method, as documented quite well by Wampold (2001). A critical review of CBT also confirmed this hypothesis (Lynch et al., 2010).

Another important question is whether CBT might be helpful for individuals with psychotic symptoms who reject neuroleptic treatment. Morrison et al. (2012) conducted a exploratory trial with 20 subjects who had positive psychotic symptoms associated with a diagnosis within the "schizophrenia" spectrum, who had either not been taking any such medications for at least six months or had never taken them. The cognitive therapy was focused on normalization, self-evaluation, examination of everyday life through behavioral experiments, and change of unhelpful cognitions, and behavioral patterns. After 9 months of therapy, 35% of the participants achieved a 50% reduction of symptoms on the PANSS, and another six months later half of the participants showed this 50% reduction. No patient became significantly worse during this treatment.

The same intervention was evaluated again in a randomized study with 74 patients who exhibited even more substantial symptomatology, resulting in similar effects (Morrison et al., 2014). Participants received cognitive therapy (CT) plus treatment as usual (TAU) (N=37) or TAU only (N=37). TAU consisted of regular care-coordination and psychosocial interventions, including the offer of family interventions, early intervention teams or community-based services involving irregular contact with care coordinators, and many of these participants were discharged by their clinical teams during the trial. On average, each person receiving CT utilized 13 one-hour sessions of CT over 9 months, with a follow-up period of another 9 months. The resulting effect of additional CT was moderate. Thirty-two percent of the group showed benefits immediately following the 9 months of cognitive therapy, while an additional 9% achieved good clinical results at the 18-month follow-up. The corresponding figures in the TAU-only

comparison group were only 13% and 18% at follow-up, respectively. Ten participants in each group started neuroleptic medication during the phase of cognitive therapy or the follow-up period:

> Because equal numbers of participants in each group started drugs, the effects noted are not likely to be due to drugs, especially because more participants in the treatment as usual group started antipsychotics during the initial treatment window. Examination of the improvement or deterioration in individuals who started drugs also suggests that the benefits are not likely to be attributable to antipsychotics. (Morrison et al., 2014, p. 7)

> On average, neither group deteriorated over time, in a population that has been assumed to deteriorate without total adherence to drugs. In fact, some participants receiving treatment as usual who were not taking drugs achieved good clinical outcomes, and more did with the addition of cognitive therapy. However, some individual patients not taking drugs did have deterioration and adverse events, and this finding was noted on both groups (additionally we might have missed some such events, in view of high rates of missing data and non-engagement with services. (Morrison et al., 2014, p. 7)

10.3 Integration of suitable trauma-informed therapeutic approaches

Fifty percent of patients diagnosed with schizophrenia have experienced sexual or physical abuse during their childhood or adolescence, according to a critical review (Morgan et al., 2007). Emotional abuse and physical/emotional neglect were not considered. There appears to be a specific connection between voice-hearing and traumatization, which has been documented in approximately 20 studies. Therefore, an integration of trauma-informed therapies as part of the treatment of psychosis, encompassing support for active engagement with voice-hearing phenomena, seems necessary. A variety of therapeutic approaches have been developed for this purpose, emphasizing either coping strategies (Vauth & Stieglitz, 2007), relating these experiences

to meaningful biographic and subjective context (Romme & Escher, 2008), or a therapeutic dialogue with the voices themselves (Stone & Stone, 1993; Corstens & Romme, 2005). Whenever the biographical context is taken into consideration, forced treatment—which occurs with greater frequency in this population--can be understood as experiences of retraumatization.

10.4 Non-verbal therapies, such as art and music therapy

There is a fair amount of evidence for the positive effects of primarily non-verbal creative art and music therapies, mostly on negative symptoms of psychosis. Creative "arts therapy is the only intervention that has been demonstrated to have medium-to-large effects on negative symptoms in people with schizophrenia."

"The Guideline Development Group (GDG) estimated that the magnitude of the improvement in negative symptoms associated with arts therapies was considerable. The therapeutic effect of arts therapies was shown to last (and was even enhanced) at least up to 6 months following treatment" (NICE, 2009, p. 204).

"The Guideline Development Group recognize that at present, arts therapies are the only interventions, both psychological and pharmacological, to demonstrate consistent efficacy in the reduction of negative symptoms" (NICE 2009, p. 205).

Music therapy is also effective in reducing negative as well as other symptoms, as measured by the PANSS and BPRS. It also appears to have strong positive effects on social and cognitive functioning, according to the Social Disability Schedule for Inpatients (Mössler et al., 2011). These effects seem to occur in a dose-effectiveness relationship (Gold et al., 2009; Gühne et al., 2012), which underlines the causal relationship as well as the generally low availability of such therapies in typical clinical settings.

Considering the basic ineffectiveness of neuroleptics for negative symptoms, and the additional risk of aggravating such symptoms further by adding new medications or

higher dosages, this lack is even less understandable.

In discussing the study by Alvarez-Jiminez et al. (2012) earlier, we suggested that the usual biological concept of negative symptoms is no longer tenable. The effects of these psychotherapeutic interventions support this notion even further.

10.5 Meta-cognitive training

"Individualized meta-cognitive therapy" for persons with "schizophrenia" was first described in 2010, and includes a number of materials for individualized approaches based on group experiences (Moritz et al., 2010). It is recommended that group-based approaches be introduced only following clinical stabilization. All 11 studies showed a reduction in positive symptoms with small or moderate effect-sizes soon after the end of the intervention, as well as after six months (2 studies) and 3 years (1 study). Improvements in self-confidence and quality of life tend to occur with some delay (Moritz et al., 2014b). Two out of 3 studies on individualized meta-cognitive training even show strong effects (Moritz et al., 2014a). There was also a reduction in premature conclusions and excessive confidence related to errors in thinking. Individualized training seems better suited for an improvement for those with deeply rooted and problematic cognitive styles (Vitzthum et al., 2014). None of these studies examined the effects of medication. One study in progress examines the effects of this treatment on patients who refuse neuroleptics.

> MCT aims to sow the seeds of doubt through corrective ('aha!') experiences in an entertaining, playful and collaborative manner. By presenting predominantly neutral (non-delusional) scenarios, MCT aims to shake (some of) the cognitive foundations of delusions, which is hoped to ultimately lead to the crumbling of delusional conviction. Cognitive biases, particularly jumping to conclusions and overconfidence, are regarded as basic driving mechanisms that turn (initially) benign false judgments into perpetuated delusional systems. The various modules of MCT demonstrate to patients that complex events can have very different

explanations and are rarely determined by single causes; that evidence can change over time; and that one should not jump to conclusions or be too confident in judgments, particularly in situations with potentially momentous outcomes. This is achieved by a dialectic approach. (Moritz el al., 2014)

10.6 Additional alternative approaches

Stastny & Lehmann (2007) provided a good overview of the broad spectrum of alternative approaches that are being developed and tried in various countries. The most important are listed in the table below:

Author	Approach
Regina Bellion	How we discovered the Soteria principle
Ulrich Bartmann	Running from the crisis
Wilma Boevink	Survival, the art of living and knowledge to pass on: Recovery, empowerment and experiential expertise
Rufus May	Reclaiming mad experience. Establishing unusual belief groups, and evolving minds public meetings
Marius Romme, Sandra Escher	Intervoice. Accepting and making sense of hearing voices
Hannelore Klafki	The voices accompany my life
Maryse Mitchell-Brody	The Icarus Project. Dangerous gifts, iridescent visions and mad communities.
Michael Herrick, Anne Marie DiGiacomo, Scott Welsch	The Windhorse Project
Petra Hartmann, Stefan Bräunling	Finding common strength together, The Berlin Runaway House
Sheri Mead	Trauma-informed peer-run crisis centers
Giuseppe Bucalo	La Cura, a Sicilian way to antipsychiatry
Theodor Itten	Psychotherapie instead of psychiatrie? A no-brainer.
Karyn Baker	Families, a help or hindrance in recovery?

Table 12: A list of alternative approaches for treating psychotic experiences.

11. Conclusion

11.1 Contextual framework

Treatment services must be appropriate and competently run in order to achieve the lowest possible dose of neuroleptics, and thereby forestall drug-induced toxicities to the greatest extent possible—an ethical condition for medical practice. This knowledge has apparently not yet reached mainstream psychiatry as well as third-party payers. Reputable international researchers call for a paradigm change (Morrison, 2012; Tyrer, 2012). Not every patient with a diagnosis of "schizophrenia" appears to need a neuroleptic, and everyone should be entitled to make an informed choice in this matter. Even the UN Convention on the Rights of Persons with Disabilities could be seen as supportive of securing this right. "Nearly every major pharmaceutical company has either reduced greatly or abandoned research and development of mechanistically novel psychiatric drugs" (Fibiger, 2012). Improving psychosocial and psychotherapeutic services, and assuring that as many mental health professionals as possible are provided with a high level of appropriate knowledge, seems to be the main way to improve the current situation.

11.2 Summary

Due to the fact that many side effects are dose-related and that a necessary D2-receptor blockade can be achieved with remarkably low doses, it is astonishing how rarely this threshold is adhered to in clinical practice. "Overshooting" seems to be the rule of the day. To begin acute treatment with high dosages is neurobiologically misguided. In order to find the minimal dose for an individual patient, we must begin with a level close to the lowest possibly effective dose, followed by gradual increments every few weeks whenever clinical effects are inadequate.

The fact that there are no randomized studies that identify dosages below 3 mg haloperidol-equivalents, while only randomized studies are currently being considered for inclusion in treatment guidelines, means that the recommended lower limits are usually too high.

Since no differences in the therapeutic blockade of D2 receptors have been identified for individuals deemed "resistant" to neuroleptics, there is no rationale for using high dosages or polypharmacy in such situations. Under the influence of neuroleptics, dopamine receptors are transformed in counterproductive ways due to dose-related multiplication and sensitization (Samaha et al., 2008). As a result, we witness a continuous rise in the "necessary" dosage over the course of treatment (Ho et al., 2011), while the proportion of patients with residual symptoms in spite of neuroleptic treatment ("partial responders") also tends to grow. This can be averted through low dosing, and presumably also by delayed administration every 2nd and 3rd day, without loss of effectiveness. Beyond this, early attempts at guided reduction and discontinuation are useful for determining the lowest possible dose in everyday life and making frequent adjustments if needed.

All of these things can be best achieved by community-based teams that provide relational/psychological continuity. The foundation for high-quality treatment of psychosis is a complex and focused psychosocial treatment model. In such a model, neuroleptics are only prescribed selectively and can usually be given in low doses. They complement the psychosocial treatment only when the former does not seem to suffice on its own. A broadly successful implementation requires that current treatment systems be refocused around the following core elements/interventions:

- Systemic, team-based early intervention within the natural life-context of the clients that involves families and social networks in the therapeutic work from the beginning.

- Relational/psychological continuity provided by these teams over several years, or for as long as it appears necessary to all parties.

- "Experts from experience" are integral members of such teams.

- A small residential structure, with trauma-informed and supportive milieu for individuals with psychoses, should be available as needed. Non-professionals and experts by experience are particularly effective team members in such a setting.

- Hospitalization as a secondary option only.

- Individual psychotherapy should be accessible whenever desired by the client. The fit between client and therapist seems more salient that the particular therapeutic method employed. Trauma-informed elements should be integrated psychotherapeutically. There should be close collaboration between the individual psychotherapist and the assigned team.

- Non-verbal psychotherapeutic approaches such as art, music, or dance therapy should also be available.

- Support within the domains of employment or education should be provided in an integrated or consultative fashion, aiming for the earliest possible placement into appropriate educational settings or work opportunities in the open market.

- All other interventions are in our opinion secondary. The rate for avoidance of neuroleptics altogether, and their dosages when used, is the main criteria for treatment quality.

In this text, we have avoided commenting on the pharmaco-industrial complex and its relationship to psychiatry. Whoever wishes to inform themselves about the impressive and decisive position regarding this issue presented by Peter GØtzsche, a founder of the Cochrane Collaboration, can access it through this link: http://www.madinamerica.com/2013/11/peter-gotzsche-2/

Glossary of Antipsychotics

Second-Generation Neuroleptics

Generic Name	Brand
Amisulpride	Not available in U.S.
Aripiprazole	Abilify
Clozapine	Clozaril
Olanzapine	Zyprexa
Palperidone	Invega
Quetiapine	Seroquel
Risperidone	Risperdal
Lurasidone	Latuda
Ziprasidone	Geodon

Depot Neuroleptics

Generic Name	Brand
Flupentixol	Not available in U.S.
Fluphenazine	Prolixin Decanoate
Aripiprazole	Abilify Maintena
Haloperidol-Decanoat	Haloperidol-Decanoate
Paliperidone	Invega Sustena
Risperidone	Risperdal Consta
Olanzapine	Zyprex RelPrevv

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