Treatment-Resistant Schizophrenia and Psychosis

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***Abstract*—Schizophrenia is a very debilitating mental health condition in all areas of life. However, for a majority of cases it has become highly treatable and full remission should be the objective of treatment. However, in a significant minority of patients the first treatment attempts do not work. This article explores some of the available options and paths that can be taken.**

Every treatment should include both medication and psychotherapy to optimize treatment success. Whether from the biological or psychological side, recovery in the case of schizophrenia and other forms of psychosis means helping the patient build better and more adaptive internal and external communication patterns and better awareness of the distinctions between them.

***Index Terms*—schizophrenia, treatment resistant, treatment, medication, psychotherapy, psychiatry**

I. Introduction

TREATMENT RESISTANCE is one of the most important clinical challenges in the pharmacological management of schizophrenia. Roughly one out of four patients with schizophrenia do not respond adequately to an initial antipsychotic trial. Tailoring the medication, possibly a combination of agents, to the needs of the individual patient becomes even more important if a treatment plan does not work or causes side effects that reduce the quality of life. At the same time, it is also important not to overlook the psychological side of restoring the patient to mental health. As we will see, a focus on internal and external communication plays important role in both psychotherapy and the use of medication.

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II. Diagnosis

Most treatment guidelines require the failure of at least two antipsychotic trials with different compounds, including at least one second-generation antipsychotic, in adequate dose over a period between 2 and 8 weeks before treatment resistance can be assumed.

Most clinical trials request non-response to at least two previous antipsychotic trials (chlorpromazine equivalents between 400 and 1000 mg/day) for at least 6 weeks. Still relevant are also the 'Kane criteria' which were introduced in 1988 which require that a patient has been non-responsive to at least three periods of treatment in the preceding 5 years with antipsychotic agents (from at least 2 different chemical classes) at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and without any period of good functioning within the preceding 5 years.

For proper functioning in everyday life a patient needs to be able to communicate with the world actively, make sense of it and integrate into a social network of relationships. In the past a lack of improvement primarily in the positive symptoms of schizophrenia was considered, while this has shifted more to include now also social functioning, for example. The level of competence in social interactions, whether at home or at the office, is important, because a lack of it can make life more stressful, lead to a lesser sense of control and confidence n the world and cause withdrawal, which then often results in a worsening of psychotic symptoms.

III. Neurobiology

It is interesting to note that a neuroimaging study using [18F]-DOPA positron emission tomography scanning examined the underlying neurobiological pathophysiology of resistance to antipsychotic medication by comparing non-responsive patients with those who had responded adequately to antipsychotics and healthy volunteers. In this investigation, the dopamine synthesis capacity was lower in participants with treatment-resistant schizophrenia than in those with sufficient response to antipsychotic medication. Moreover, there was no significant difference between participants with treatment-resistant schizophrenia and healthy volunteers.

These findings suggest that a medication aimed to achieve a blockade of dopamine receptors may be effective especially in patients who have an elevated dopamine synthesis capacity but less efficacious in patients with relatively normal levels of dopamine synthesis capacity and in treatment-resistant patients.

IV. Causes of treatment resistance

If a patient does not respond adequately to the first administered antipsychotic drug, the following steps should be considered:

A. Diagnosis

Re-evaluation of the diagnosis of a schizophrenic disorder. Particularly severe personality disorders, mania or depressive disorders with psychotic features are in their acute phase sometimes difficult to distinguish from schizophrenia. Similarly, brain tumors and encephalopathies can cause psychotic states. Furthermore, substance abuse might need to be ruled out. Comorbidities such as affective disorders or obsessive-compulsive disorder should be considered, as these may contribute to treatment resistance.

B. Non-Compliance

Non-compliance or non-adherence can be considered as a major reason for non-response to antipsychotic medication or to a psychotherapy. It has been assumed that more than half of the patients do not take the prescribed medication correctly. To objectify compliance and adherence in terms of medication intake, plasma levels should be considered. The use of long-acting injectable antipsychotics can sometimes be a possibility to rule out non-adherence. However, this should always be discussed in depth the patient, who should see more benefits than disadvantages in it.

Non-compliance is usually a consequence of a communication problem. From whatever angle the non-compliance arises, even if there is a resistance to getting better as far as the condition is concerned, most patients would rather suffer less in their daily lives. This may mean having to address fears or other emotions or thoughts that cause resistance to various forms of therapy and can cause a prescriber of psychotherapist to misinterpret it as a lack in motivation towards therapy.

C. Dose

If the dose is not adjusted adequately for the individual patient, ineffectiveness or more side effects can be the consequence, which can potentially both reduce the compliance even further. Of course, this means that the effect profile of the antipsychotic and the dose both have to be tailored to the individual patient specifically. This requires detailed knowledge of the patient as well as of the available treatment options, both medically and psychologically.

Patients with first-episode schizophrenia and older patients often require lower doses. The onset of symptom improvement may vary considerably between individual patients. International pharmacological guidelines recommend a minimum medication period between 2 and 8 weeks until in case of insufficient response a change of the treatment strategy should be considered.

Agid et al showed that the highest symptom reduction can be observed already within the first week of medication and then decreases consistently. All in all, the study results suggest that in case of no symptom improvement within the first 2 weeks of treatment in adequate dose, no long-term response to therapy can be expected. In patients with a history of at least one non-response to antipsychotic treatment a significant symptom reduction usually occurs within the first 4 weeks.

1) Metabolization

Variations in metabolization rates among individual patients are one reason why very different dosages can be required in each case. While blood levels of psychiatric medication are often not assessed, particularly in the case of antidepressants, in medication to treat psychosis or bipolar disorder this is often recommended and necessary.

Polymorphisms in the cytochrome P450 enzyme system can significantly influence available blood levels in psychiatric medication. Greater enzyme activity and can lead to significantly lower medication blood levels, while reduced enzyme activity can cause a slower metabolization. About 5% of the population have a relevant reduced enzyme activity, while 1% have a significantly elevated one.

Smoking induces the cytochrome P450 isoenzyme 1A2, leading to lower blood levels of a drug, which may require an increase in the dose. Olanzapine, clozapine and other drugs can be affected. Also, if a patient suddenly stops smoking, or reduces the tobacco consumption significantly, the blood levels of psychiatric medication can go up considerably leading to an increase in side effects.

2) Drug Monitoring

There is no convincing evidence for a clear relationship between drug concentration in the blood and antipsychotic response. If feasible, a gradual titration of the medication is often the best approach to find the individual therapeutic window in which the needed positive effect is achieved with no or a minimum of side effects. In other words, the dose should maximize the quality of life.

Plasma level measurements may be useful in clinical practice in case of inefficacy of the medication or occurrence of severe adverse effects even at low doses. Drug concentration in the blood should be determined in the steady-state which is attained for most of the psychopharmacological drugs after approximately five elimination half-lives after the first medication intake. This corresponds for most antipsychotics to one week after achievement of the maintenance dose.

Blood for drug concentration measurement should be withdrawn ideally before ingestion of the morning dose which is usually 12–16 h (or 24 h if the drug is given once daily in the morning) after the last medication intake.

3) Target Doses

Recommended target doses are subject to change over time. The following provides a list of dosages that have been mentioned in the literature (in mg/day), although this may have changed in the meantime, and a drug may have also been discontinued or lost its approval status. It is always important to check the current literature, recommendations and guidelines.

First-generation antipsychotic drugs

Chlorpromazine 300–600
Flupentixol 5–12
Fluphenazine 5–15
Haloperidol 5–10
Perphenazine 12–24
Trifluoperazine 10–20

Second-generation antipsychotic drugs

Amisulpride 400–800
Aripiprazole 15–30
Clozapine 200–500
Olanzapine 10–20
Paliperidone 6–9
Quetiapine 400–800
Risperidone 4–6
Ziprasidone 120–160
Zotepine 100–300

Some groups of patients require normally lower doses for achieving response, for example patients with first-episode schizophrenia as well as older patients.

4) Dose increase

A dose increase above the approved dose range should normally not be considered. There are few potential benefits, if any, and the adverse effects of antipsychotics can be substantial. Even some of these side effects may not appear dose dependent in the approved dose range, this does not necessarily mean this is also true at doses beyond this dose range. Among the older antipsychotics, clinical studies and systematic reviews concluded that a daily dose more than 800–1000 mg chlorpromazine equivalents (or even lower) does not improve antipsychotic efficacy but is associated with an increased incidence of especially extrapyramidal adverse effects. There is also little data to support going outside the approved dose range for newer atypical antipsychotics. Switching an antipsychotic, or in some cases augmentation and combination therapies, are usually the better option.

However, having said this, individual patients may respond to a high-dose or even off-label treatment. Patients with polymorphisms in the cytochrome P450 enzyme system, for example, can probably benefit from a dose increase when their drug concentration in the blood is below the effective therapeutic range in a standard dose.

When a high-dose therapy is initiated in a patient, it should be closely monitored, both on the somatic and psychiatric sides, and evaluated in short intervals, particularly in the beginning. One should be vigilant for side effects and routinely justify the use of the higher dose.

D. Switching

The usual recommendation is to taper off the dose of the first antipsychotic gradually while simultaneously increasing gradually the dose of the second one, hence its name ‘crossover titration’. Alternatively, the dose of the first antipsychotic can be maintained at the same dose while the dose of the second compound is increased gradually to a therapeutic level and only then the dose of the first agent will be decreased (‘overlap and taper’). However, this carries a greater risk of a neuroleptic syndrome and should be reserved for cases where a patient could be a danger to himself or others.

SELECTING A NEW ANTIPSYCHOTIC

It makes sense to select a drug with a different receptor affinity profile. For example, the more serotonergic olanzapine or quetiapine may be chosen, if the current drug has less serotonergic affinity, such as aripiprazole or a particularly high affinity to dopamine receptors such as amisulpride, risperidone at higher doses or a first-generation antipsychotic agent. Of paramount importance in the selection process is to keep in mind the individual needs of the patient, such as whether more sleep-inducing properties or less sedation increase the quality of life, or whether an increase in appetite is desirable or undesirable.

There are numerous examples that support keeping the receptor affinities of individual substances in mind when switching. In the ‘Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)’, non-responders to perphenazine benefited significantly more from a switch to olanzapine or quetiapine compared to risperidone. Both perphenazine and risperidone are characterized by high antidopaminergic

properties and therefore, which probably reduced the potential benefits from a switch.

Even if a switch makes psychopharmacological sense, the benefit in the real world may be lower than expected. Positive effectiveness trials are derived from data with nonresistant patients and these results cannot be automatically extrapolated to patients who have no or inadequate response to previous antipsychotic medication.

In one study, the authors randomized non-responders to an initial 2-week monotherapy with risperidone to either a switch to olanzapine (10–20 mg/day, n=186) or continuing the same dose of risperidone (2–6 mg/day, n=192) in the control group. After 10 weeks, a small but statistically significant between-group difference could be identified in favor of switching to olanzapine. The mean difference on the 'Positive and Negative Syndrome Scale' was 3.5 points.

The rational for a switch may be even lower in older high potency antipsychotics. In a randomized study by Kinon et al, non-responders to a 4-week monotherapy with fluphenazine 20 mg/day (n=115) were randomly assigned to either a group in which the medication with fluphenazine was continued in a constant dose, one where the dose was escalated to 80 mg/day, and one which was switched to haloperidol 20 mg/day. There was no significant superiority in any of the groups.

Thus, in summary, there is not that much support for a switch from one antipsychotic to another. On the other hand, in clinical practice there can be significant benefits from switching in terms of symptom remission and a much improved side effect profile in individual cases. The factors that are at play here are not entirely understood yet.

Although the efficacy of clozapine in the pharmacological management of treatment-resistant schizophrenia is undisputed and sufficiently proved, some ambiguity remains regarding the status of other antipsychotics in treatment-resistant conditions. Significant effect sizes were found for the second-generation antipsychotics risperidone, olanzapine and amisulpride, for example. However, these data were mainly derived from non-resistant participants.

Uncertainty still exists which antipsychotic should be given when clozapine treatment is not tolerated or is not feasible because of the occurrence of adverse effects. Some treatment guidelines recommend treatment with olanzapine or risperidone. In clinical trials with treatment-resistant patients, both compounds were not significantly inferior in direct comparison to clozapine and were able to achieve higher effect sizes compared to first-generation antipsychotics.

CLOZAPINE

Clozapine has largely remained the gold standard in the pharmacological treatment of refractory schizophrenia. However, given the 1% risk of agranulocytosis and the various other adverse effects, though the latter are also not uncommon with other antipsychotics, clozapine may be used only after at least two failed previous treatment attempts with two other different antipsychotics in adequate dosage and duration.

In a network meta-analysis comprising 212 randomized trials and a total of 43,049 patients with schizophrenia, clozapine achieved the highest effect size in terms of antipsychotic efficacy followed by amisulpride, olanzapine and risperidone. However, studies with therapy-resistant patients were excluded in this analysis and clozapine was superior even in non-resistant participants. However, the authors discussed that the superiority of clozapine stems mainly from comparisons with first-generation rather than second-generation antipsychotics.

Similarly, clozapine resulted superior to other second-generation antipsychotics in a phase II study of the CATIE trial and in the 'Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 2)' when analysing schizophrenic symptom improvement.

E. Combination strategies

The effectiveness of combination therapy is probably less than previously thought. A frequently investigated combination is clozapine, which has rather low antidopaminergic properties, with antipsychotics that have a high affinity for dopamine receptors.

In their meta-analysis comprising 14 RCTs on combinations of clozapine with second-generation antipsychotics, Taylor et al found a small but statistically significant superiority of the combination treatment compared to placebo. In another meta-analysis by Sommer et al, stratified according to the various compounds combined with clozapine, a significant positive effect was determined only for sulpiride (based on a single trial) but not for amisulpride, aripiprazole, risperidone and haloperidol.

Barbui et al found a significant superiority of clozapine combination with second-generation drugs only for randomized open studies but not for double-blind trials. Correll et al compared in their meta-analysis an antipsychotic combination with monotherapy whereas the previously described meta-analyses exclusively examined clozapine cotreatment. The combination therapy was superior to monotherapy in terms of all cause discontinuation and dropouts due to inefficacy. However, it must be noted that many Chinese studies were included that did not comprise only treatment-resistant participants. Furthermore, in this meta-analysis a publication bias cannot be ruled out.

Concerning the partial dopamine agonist aripiprazole, there is no convincing evidence that a combination treatment with this compound causes any improvement in schizophrenic symptoms, but it seems that cotreatment with aripiprazole can reduce antipsychotic-induced metabolic adverse effects as well as elevated serum prolactin levels. Antipsychotic monotherapy should be generally preferred and sought,

although individual patients can certainly benefit from a combination treatment. In this case, efficacy, drug interactions and the occurrence of adverse effects should be closely monitored and, in case of inefficacy of the combination strategy, monotherapy should be considered again. In particular, the risk of metabolic side effects and all-cause discontinuation may increase significantly by administering antipsychotic combinations.

1) Augmentation strategies

Augmentation treatment means the use of two drugs of different classes in parallel, for example the coadministration of an antipsychotic drug with an antidepressant, mood stabilizer or benzodiazepine. Many compounds have been investigated as augmenting agents of antipsychotics without demonstrating convincing efficacy in treating schizophrenic symptoms. Evaluated agents have been, for example, acetylcholinesterase inhibitors, β-blockers, carbamazepine, lithium, valproate and memantine. Although benzodiazepines may be indicated in short-term treatment of acutely agitated patients, there is no evidence for the use of benzodiazepines as long-term adjunctive treatment to improve psychotic symptoms. They may even worsen some negative symptoms over the long-term, such as emotional flattening or cognitive impairment, and lose their effectiveness as the patient develops tolerance.

Sommer et al found in their meta-analysis a significant positive effect of lamotrigine augmentation in clozapine-resistant schizophrenia but this effect disappeared in a sensitivity analysis after exclusion of an outlier study with high effect size and small sample size. Similarly, a significant positive effect of topiramate on schizophrenic positive symptoms diminished after removal of an outlier study. Very recent meta-analyses support augmentation with aspirin or other drugs with effects on the immune system, but these findings are in our opinion not yet ready for transfer into practice.

As with the combination treatments, there is not enough evidence to advise the general use of pharmacological augmentation strategies in treatment-resistant schizophrenia. A possible increase of adverse effects and drug interactions must be considered. Augmentation strategies should be regarded preferable for the treatment of specific target symptoms such as benzodiazepines in highly agitated psychotic patients or antidepressants for the treatment of comorbid depressive symptoms or marked negative symptoms. Augmentation and combination treatments should be discontinued in case of inefficacy and antipsychotic monotherapy should be sought again.

F. Side Effects

To assess the progress of treatment, it is important to distinguish between side effects and symptoms of the underlying condition. However, this is often not so easy. For example, akathisia can be misinterpreted as mental agitation or parkinsonism may mimic schizophrenic negative symptoms. Sometimes the only way to find out is to change the dose of the medication or to add another substance which is known to work if the observed symptom is a side effect of the medication.

V. Psychotherapy

A. Psychosis, Information Processing and Communication

Psychosis is often used descriptive term for the hallucinations, delusions and impaired insight that may occur as part of a psychiatric disorder. More correct would be to use it to describe the alterations in information recognition and processing. Some symptoms can be due to a misinterpretation in the source of the information, or as a misinterpretation of one's own position relative to the source of information, while others appear due to a misinterpretation of the messages.

Psychotherapy can help the patient to gain awareness of internal and external communication patterns, which facilitates a clearer distinction between inside and outside communication and a greater sense of efficacy and mastery in using communication with oneself and others to meet needs, values and aspirations.

A perceived reality works in which communication, the exchange of meaningful messages, works. One's perception of reality should facilitate communication with oneself and others, rather than impeding it. In other words, a perceived reality should help in a meaningful interaction with oneself and others. The symptoms of psychosis interfere with meaningful internal and external communication, and thus with needs fulfilment, which reduces the quality of life. But they also affect a patient's ability to build strong and beneficial relationships, in which meaningful communication can take place, leading to loneliness, and often withdrawal and isolation, which impedes even more with the meaningful outside communication that is not only needed for needs or value fulfilment but to experience oneself as fully human and active in the world.

Humans live at least partially in shared realities because they communicate meaningfully with each other. The advantage of adopting elements of a shared reality is that communication with others, and thus one's ability to meet one's needs, values and aspiration, becomes easier. The world also becomes safer and more predictable. Obtaining an understanding of a patient's perceived reality early in therapy improves the communication between therapist and patient significantly because they can operate from a shared reality, which makes it easier for the interaction to change

communication patterns, and as a result the real world of the patient (and the therapist). If the psychotic symptoms make meaningful communication difficult, medication assumes additional therapeutic values, but even in the most acute psychotic episode some level of communication is still possible and of severely underestimated importance for the moment, as well as for the long-term.

Psychosis affects how information is processed. Besides medication, helping people to have a different perspective on the flows of information and process them differently is an important way to treat psychosis. By helping patients to receive more information and be more perceptive to reality, they can also 'build' a reality which causes less suffering and is better suited to have their needs and wants met.

An important feature of reality is where one perceives that information is coming from. If one hears voices, internal thoughts are misinterpreted as external voices, or if one feels pursued by a secret agent, an aggressive emotion, for example, leads to an aggressive person in the outside world. Better insight into communication and learning communication skills can also help the patient to better localize sources of messages and build a more stable view and sense of reality.

Psychosis often leads to a disconnect from one's emotions, which can cause emotional flattening, although it may be difficult to distinguish which part of it is due to the underlying condition and which is due to antipsychotic medication. Working with communication in general usually helps to improve the internal communication patients have with themselves as well. This lowers the disconnect from oneself a patient may experience.

Learning to identify better the sources of information, inside one's own body and in the outside world, can help to attach the correct meaning to a sensation or a voice one hears. This can be trained in the communication space of a psychotherapeutic setting. Practicing communication and reflecting on it helps the patient to develop greater insight and sharpen his or her communication skills.

Learning about communication usually includes a theoretical psychoeducational component and a practical component. Engaging in communication can be important to increase one's confidence and skills in the process. At the same time, better proficiency in communication also makes any other learning processes easier.

1) The Communication Space

Depending on the environment we move through different communication spaces in everyday life. The communication space is the space in which messages are being sent and received. If one is talking to someone over the phone who lives on a different continent, the communication space extends to this person, while not including the neighbor in the apartment next door, unless the walls are really thin.

To a patient suffering from psychosis the communication space can be extremely large or extremely small, but it usually diverges considerably from that of other people. Thoughts, for example, can be influenced from a large distance, or, at the other extreme, a patient could fully disconnect from the environment. To someone suffering from psychosis the internal world largely determines the communication space, while other people's communication space is determined through an interaction with the environment.

In therapy, it is important to make the patient aware of the communication space he or she builds and what influences it. This is an important component of learning about communication and bringing about change through it.

2) Resources

Patients suffering from psychosis often lose a sense of their own resources because the self becomes fleeting and less accessible. In the therapeutic interaction, through the communication process a more stable distinction between the inside and outside worlds can be established, which strengthens the sense of self, and thus makes the own resources more accessible.

Using communication more optimally can, for example, compensate for various cognitive impairments which are often a part of psychosis. Certain strengths can be used better if the communication with oneself and the world around improves. Resources can also be easier felt and relied upon if one communicates better with oneself, which may include being better at identifying where information comes from, especially if it represents an emotion, what it means, and how one can react to it.

Psychosis is an abnormal condition of the mind that involves a loss of contact with reality. People experiencing psychosis may exhibit personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out daily life activities. Generally, psychosis involves noticeable deficits in normal behavior and thought (negative symptoms) and often various types of hallucinations or delusional beliefs, particularly with regard to the relation between self and others as in grandiosity or paranoia (positive symptoms).

Unfortunately, psychosis as a diagnostic term is often used after other reasons have been excluded. It may therefore be more illuminating to think of psychosis as a mental process involving changes in how information flows and how these flows are interpreted, which can occur in various psychiatric conditions.

3) Experiencing the World

Psychosis often leads to a vicious cycle which leads to less rather than more communication. Anxieties and a changed perception of reality can lead to a disengagement from it, which reduces the ability to distinguish internal from external reality even more. Practicing and discussing with the patient new ways to communicate, including new communication patterns and better reflection on them, increases the patient's ability to experience and bring about change in the world.

Next to improving interactions with others, a better identification and understanding of meaning helps to anchor the patient better in the shared reality, which makes everyday life and planning for the future easier.

4) Misinterpretation of Sources of Information

As the information can no longer be correctly attributed to an outside or an inside source, the individual experiences own thoughts coming from outside in the form of voices or people on the outside as part of internal mental processes and might experience this as people having influence on the own thoughts. From the differently perceived localization of perceptions and messages a different reality is constructed. Since the pieces often do not integrate as well into it as in the shared reality, gaps can result, which then lead to fears, often of an intense and existential nature.

5) Misinterpretation of Messages

A misinterpretation of messages is different from a misinterpretation of the sources of information, but they often seem to go hand in hand in psychosis. The conviction that someone is pursued by a neighbor, who is a spy, can be a misinterpretation of an emotion towards this neighbor as a (real) outside event, while a smile from the neighbor in the hallway can be interpreted as her satisfaction about having made a plan to harm the patient, which would be a misinterpretation of her original message of saying 'Hi'.

A misinterpretation of messages usually occurs with respect to the universe of the patient, emotionally and perceptually. When focusing on the communication in therapy, it is therefore important to first get a sense for the universe the patient finds himself or herself in, both perceptually and emotionally. This information allows the therapist to build a better rapport with the patient, since the messages from the therapist will be interpreted by the patient within the context of this universe.

B. Communication-Focused Therapy (CFT)

Communication-Focused Therapy (CFT) was developed by the author to focus more specifically on the communication process between patient and therapist and use it to help the patient acquire more insight and better skills in the own internal and external communication. (Haverkampf, 2010) The central piece is that the sending and receiving of meaningful messages is at the heart of any process leading to changes in thoughts or external situations. CFT has been developed by the author for several mental health conditions, including depression, OCD, social anxiety, ADHD, eating disorder, bipolar disorder, and others.

CBT, psychodynamic psychotherapy and IPT help because they define a format in which communication processes take place that can bring about change without focusing on them. CFT tries to be more efficient in a therapeutic sense by focusing on them more directly.

1) Understanding Psychosis

In psychosis the internal and external worlds cannot be distinguished as accurately anymore. They seem to blend into each other. This can cause various symptoms that are then summarized as 'psychotic'. However, each symptom should make sense in the context of the patient's communication patterns as well as the life experiences and emotions the patient faces, which influence the content of the psychosis. Having an understanding for what is happening, is important because it also helps make the patient feel more secure.

Another feature of psychosis is a more or less strong divergence from the patient's perceived world from the shared reality, maybe one aspect which allows artists with intermittent moderate psychosis to paint stunning works of art. This divergence is largely driven by emotions or thoughts which become disassociated from the fabric of the patient's self and personality.

2) Facilitating Communication

At the start when treating psychosis, it may appear difficult to engage in a constructive communication process. However, meaningful information usually elicits a reaction in living organisms over time. Even in mental states which seem very closed off, the brain still receives and processes information streaming in from the external world. Persistence, often combined with effective antipsychotic medication as a supporting instrument, usually help to get patients to a point where they get used to exchanging meaning with the other and fears decline, which facilitates communication even more. It is important to remember that it is almost impossible not to communicate.

3) Knowing Where Information Comes From

In the end, the patent should also have a better sense of communicating and knowing where information comes from. Not only does this help this reduce the divergence between the experienced world and the shared world, but it also helps to

use information and communication better. Being able to identify a source of information can make it easier to identify meaning and respond to it. This helps build a stronger sense of self, better relationships and imparts greater confidence in dealing with everyday life as well towards fulfilling own aspirations. Greater insight and skills into communication can accomplish this.

4) Autoregulation

Communication is an autoregulatory mechanism. It ensures that living organisms, including people, can adapt to their environment and live a life according to their interests, desires, values, and aspirations. This does not only require communicating with a salesperson, writing an exam paper or watching a movie, but also finding out more about oneself, psychologically and physically. Whether measuring one's strength at the gym or engaging in self-talk, this self-exploration requires flows of relevant and meaningful information. Communication allows us to have a sense of self and a grasp of who we are and what we need and want in the world, but it has to be learned similar to our communication with other people.

5) Unhelpful Communication Patterns

Overtime, due to a mix of nature and nurture, through interactions with the environment, humans learn, practice and develop communication patterns to get own needs, values and aspirations met, that become increasingly automatic and seemingly second nature to the person. One task of psychotherapy is to help a patient develop awareness of the own communication patterns, particularly those where changes can significantly improve the quality of life.

6) Meaningful Communication

When an individual suffers from psychosis, a first important step is to help the patient see meaning in the communication process, particularly a relevance to own needs and interests. This helps to build and maintain the motivation which is necessary for a communication oriented therapeutic process. It also helps the patient build a greater sense of efficacy when interacting with his or her environment.

Since the communication process is usually significantly affected in psychosis, it may seem even more difficult to identify and interpret meaning in the messages. This is, however, not necessarily the case. To the contrary, patients suffering from psychosis often see meaning in the world in places where others do not. The drive to see meaning and meaningful connections in information from oneself and the world has not decreased, but the supply of information has.

7) Learning about Communication

The first step is to learn about communication, to see how it works, what its constituents are and the purposes it can serve. Often it helps to go through examples that may be of special relevance to the patient. Analyzing them and looking at different options and different outcomes help to illustrate to the patient the importance of the process.

For the learning process, it is important that the therapist has a sense of the patient's perceptual and emotional world. This enables the therapist to use communication styles and messages which are interpreted by the patient not as hostile, deferential or lacking in empathy. Early in the therapeutic process the interaction should help to build a strong and stable therapeutic relationship. This is already part of the learning process and should come first.

8) Observing Communication

Splitting up communication and being able to identify its components helps to observe the process and the variations, large and small, in it. Observing is not only a learning experience, but also helps to develop interest for it and see the possibilities in influencing and shaping interactions with others. An interaction can exist in many shapes and forms, while the underlying communication processes adhere to common rules and laws. It helps the patient to appreciate the common underlying mechanisms, which can increase trust in the process and a sense of stability in the world, and, at the same time, to see an interaction as a dynamic group of interacting communication events.

Important is that the patient learns to be able to look at the bigger picture, to observe communication as it takes place, whether it involves the patient or not. This essentially requires being able to take a step out and away from oneself to observe the dynamic without engaging in it at the same time. Over time, this becomes automatic enough that observation and engagement can alternate in one's awareness so quickly that they seem to be simultaneous.

A patient can learn about communication if the therapist reflects and comments on what happens in the communication space between the patient and the therapist. This teaches the patient patterns and skills through the expertise and experience of the therapist. However, it requires that the therapist has this expertise and experience. Especially for a psychotic patient, it is important to show this not just in theory, but also in practice through trying out new communication experiences which then translate into new perspective of the world and oneself.

9) Experimenting

Experimenting with communication in its different flavors can give the patient a greater sense of effectiveness with respect to the environment as well as oneself. It gives patients

a greater sense of being in control, which is helpful because patients with psychosis often experience helpless and hopelessness, which can also cause some of the sudden emotional outbursts seen in severe cases of psychosis, such as schizophrenia.

A gradual increase in the scope or difficulty in the scope of experimentation probably works best. It can start with little everyday encounters and end with dating. People generally feel more vulnerable the more they feel they expose about themselves. For patients suffering from psychosis this anxiety is much greater, because they sense that their perceived world and the shared reality diverge. Own emotions may also feel real, which makes their visibility to others even more risky. The fear of getting hurt at the core of one's mental structure is universal, the hurt, however, seems more devastating in a patient suffering from psychosis because the structure is already under considerable stress.

10) Reflection

The newly gained knowledge and skills around communication needs to be processed, which can help increase the confidence and sense of effectiveness in the world. This should not be solely about control, but more about seeing oneself as a part of something bigger which is not something to be afraid of but helps individuals to address and meet their needs and wants.

11) Identifying Meaning in the World

Fears brought about by the divergence of the perceived reality from the shared reality lead to social isolation and withdrawal, which in turn reinforce feelings of fear and loneliness or frustrations. To break this cycle, it is helpful to help the patient to find more relevance in aspects of the shared reality. This is usually not a process which happens from one day to the next, but over time leads to a closer alignment of the patient's perceptions and intentions with the shared reality

Communication helps in identifying and finding meaning, either communication with oneself or with others. The exchange of messages is like a learning process in which meaning can be identified, found and accumulated. Through meaningful interactions one accumulates more meaning, more connectedness with oneself and the world and reduces the need for thoughts and behaviors which are triggered by fears, guilt, self-blame and other negative emotions. This also helps against depression and anxiety.

There are essentially two techniques to help the patient with identifying and interpreting relevance and meaning in the world. One is by directly discussing with the patient what he or she needs and wants and how this can be met in the world, the second is by helping the patient to have better interactions with the environment which make it easier to see relevance and meaning in the environment. Usually, a combination of both leads to a good outcome.

12) Increasing Interactions

Perceiving more meaning also makes interacting with others and oneself more meaningful. This has a positive effect on one's interaction patterns, how and in which ways one relates to one's environment and exchanges messages with it. As the anxiety about interactions with others decreases, it should become easier to become more socially involved with others, at least to the extent which would feel comfortable to the individual also without the illness.

In the beginning this often requires reducing fears associated with situations or people that are a result of the psychotic experience. Different interpretations of information and the sources of information lead to the perception of a world which is not only less stable but seems to contain real threats, even if the latter ones are just own emotions or thoughts which have manifested as real to the patient. Meaningful interactions with the world can reduce the divergence of realities and the fear, because they stabilize the patient's experience in the world. To be meaningful the interactions should be an exchange of messages that are relevant to the patient's interests, values or aspirations. This is one reason why it is important to discuss with the patient and get a sense for the patient's needs, wants and values. The next step is then to help the patient find and make interactions that are helpful and meaningful to him or her. With the additional focus on communication, whether in a therapeutic session, internal thoughts or between the patent and others, interactions should become easier and the fears of them lower.

13) Values, Needs and Aspirations

Often, individuals suffering from psychosis become uncertain about what is important to them and the fit between these values and interests and their current life situation. In all areas of life, having one's needs, wants and values met, leads to a higher quality of life. If one values helping others in a specific way, it is important to find ways to engage in this activity, because it will result in a positive feeling. Harm to oneself and others is usually a consequence of some disconnect with one's own feelings, needs, wants and values. Burnout or verbal abuse of another person may be examples.

The change in one's relation with oneself and the environment, as well as the resulting change in the sense of self, make is usually harder for an individual suffering from psychosis to identify correctly the own needs, wants, values, and aspirations, partly out of fear that they could disturb a fragile feeling reality even more. In this situation, it is helpful to help the patient understand that connecting with them actually adds stability, rather than taking away from it. One way to reduce the fear of getting closer to and identifying key

parameters about oneself is to help the patent emotionally reconnect. The emotions are the sum of vast amounts of information, such as a feeling of happiness as the product of perceptions of a situation and associated thoughts, and can, if they are owned by the patient, lead to a greater feeling of stability. Helping the patient to notice and identify them more accurately can lower fears and the make the inner world, and thus also the outer world in psychosis, seem more predictable. It is important to add in this context, that emotional instability is not so much due to a too much of emotions, but a consequence of impairments in a patient's internal communication with the own emotions. The inability to read the emotions accurately leads to the sense of instability, or even the emotional and existential 'void' which is so prevalent in a patient with borderline personality disorder.

14) Meaningful Messages as the Instrument of Change

Communication is the vehicle of change. The instruments are meaningful messages which are generated and received by the people who take part in these interactions. In a therapeutic setting, keeping the mutual flow of information relevant and meaningful brings change in both people who take part in this process. The learning curve for the patient may be steeper in certain respects because he or she spends less time in this interaction style than a therapist.

The main objective is that patients can make communication work for themselves on their own. Looking at communication patterns and how meaning is generated in a therapeutic session should not only help with a concrete situation or problem in the moment but provide the tools to work with a multitude of situations or problems in the future. The key to build motivation and to use communication processes, is to understand that meaning, information about information which is relevant to and resonates with the recipient of the message, is very much at the heart of it. Becoming better at sending and receiving, interpreting and working with meaning can make the world for an individual suffering from psychosis more stable and broadens the scope of change that can be brought about relative to the world and oneself. Better insight and skills around communication and meaning take some time but can have a lasting beneficial effect for and individual suffering from psychosis.

VI. Conclusion: The Better Combination

The standard treatment approach in most cases should be to combine psychotherapy and medication. The medication often makes psychotherapy possible in cases of more severe psychosis, while psychotherapy can increase the compliance for medication and treatment in general. Each on its own contributes significantly to less symptoms, less adverse effects of the medication and a higher quality of life in general. However, in combination they can have synergistic effects over the short- and the long-term that significantly go beyond the sum of each of them. While medication s usually the first-line treatment in acute psychosis, in the long run psychotherapy can be a powerful treatment method with an enduring effect.

Conflicting Interests

The author reports no conflicts of interest.

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