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Schizophrenia: Prevention of relapse and re-admission to
psychiatric hospital after treatment.

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague, 2010-03-25

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Schizophrenia: Prevention of relapse and re-admission to psychiatric hospital after treatment.

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Introduction

Schizophrenia is a very disabling psychiatric disorder with many potentially disabling symptoms.

My personal interest in psychiatry combined with the fact that there are relatively non- standardized approaches to treatment options of schizophrenia, prompted me to write this review article. This to establish if there are clinical evidences that favors one/more approaches over other ones. I was surprised about the vast amount of clinical studies and trials that had been done on this topic, something which contributes to the certification of available knowledge in review articles.

Schizophrenia and relapse symptoms

Symptoms of schizophrenia and related psychotic disorders are great contributing factors to the patient's outcome and success in preventing relapse; Anxiety, withdrawal and isolation from society, friends and family, but also from the team/institution assigned to follow up the patient, lead to deterioration and worsening of symptoms ²⁾. Other symptoms giving clues to relapse include changes in thought processes, behavioral changes and frank psychotic delusions and hallucinations ³⁾.

There are today two main systems for classifying schizophrenia; ICD-10 (European countries) and DSM-IV (U.S.). Both have similar criteria for the diagnosis of schizophrenia.

The symptoms of this disabling illness include changes in a person's thought, perception, affect and behavior, often classified into positive and negative symptoms;

Positive symptoms contributes with something “new” to the mind; delusions, hallucinations and thought disorders. These are typically regarded as manifestations of psychosis.

Negative symptoms represent loss or absence of normal traits or abilities; blunted affect/emotions, poverty of speech (alogia), inability to experience pleasure (anhedonia), decreased desire to form relationship (asociality) and decreased motivation (avolition). Rare cases of catatonia have also been described ⁶¹⁾.

Both negative and positive symptoms have a great impact on the patients, but also on the patient's family and friends (carers). However, research show that negative symptoms may contribute more to the burden experienced by both parts ⁶¹⁾. The fact that this disease contributes a great burden is no less true after patients have received proper medical psychiatric care in a suitable facility; Symptoms tend to relapse/remit in an alternating pattern after discharge from hospital or from out- patient treatment facility ²⁾.

Signs of relapse in schizophrenia may be one or more signs/symptoms arising in a prodromal period, some time (usually days to weeks) before frank and clear signs of psychosis develop and/or intervention by the health- care system is again required (see section on Identifying relapse symptoms).

This often occurs after the patient is considered treated adequately and stabilized, living a good- as- can- be- expected life with good social functioning.

The term “prodromal” symptoms is typically used to describe symptoms arising *before* the initial presentation of disease. However, in this article, as well as in most of the studies cited, “prodromal” symptoms will also include the patients with an established diagnosis of schizophrenia and related psychotic disorders.

It is important to note that not all patients experience clear- cut relapse symptoms, making detection and intervention even more challenging.

Symptoms of relapse may include gradually increased social withdrawal, increasing lack of basic hygiene, increasing disorganized thoughts or sometimes milder versions of some positive symptoms. Some symptoms are often more prominent in some patients than in other.

The prodromal period is typically followed by an acute phase marked by characteristic positive symptoms of hallucinations, delusions and behavioral disturbances such as agitation and distress.

Following resolution of the acute phase, usually due to some treatment, positive symptoms diminish or disappear for many people, sometimes leaving a number of negative symptoms not unlike the early prodromal period. This third phase, which may last many years, is often interrupted by acute exacerbations or relapses, which may need additional interventions ⁵⁹⁾.

With current treatment options there is an approximate 35% relapse rate annually from schizophrenia ³⁾, with an estimated 80% after 5 years even with maintained medication (Robinsons et.al, 1999). Chances of full remissions become less likely after each relapse (Wiersma et. Al, 1998) ²⁹⁾, with a chance of full recovery after a first episode of 14 – 20% ⁵⁹⁾.

From a health- cost point of view, relapse in schizophrenia is obviously a source of huge health- care costs every year, bordering \$2,3 billion in the U.S. ⁴²⁾. The importance of relapse prevention is also underlined by the fact, that when patients are asked to rank their needs, prevention of relapse tend to be ranked very high ¹⁾.

Shepherd, Watt, Falloon, and Smeeton (1989) found that 35% showed an increased incidence of drug- resistant symptoms following each relapse.

A 15-year follow-up study in Holland (Wiersma, Nienhuis, Slooff, & Giel, 1998) found that after each relapse, 1 in 6 patients were left with residual symptoms they did not have before ⁸⁾.

It is thus of profound importance to prevent this vicious circle and to follow up the patients adequately to prevent the relapse and re-admission to hospital.

Contents

This review article will focus on how to prevent relapse and re- admission to psychiatric hospital after the patient diagnosed with schizophrenia is considered adequately treated and is discharged from psychiatric hospital.

The article will also in some short terms cover the prevention of relapse in bipolar affective disorder, as relapse symptoms of this disorder often are of the most easily recognized among the commonest psychiatric disorders and may, if severe enough, escalate to psychosis.

It will especially be focused on the relapse program ITAREPS, a feedback- system for patients employed originally in Czech Republic since 2005.

Primary prevention of schizophrenia itself (by screening for risk factors, intervention and other programs employed before a first- time psychosis or diagnosis of schizophrenia) will not be discussed broadly, as this is beyond the scope of this article.

The results cited in this article is based on non- systematic literature searches (see “references” section).

Review

Except for the more or less standardized use of anti- psychotic medication, there are today several approaches to treat schizophrenia and related psychotic disorders; in developed countries, anti- psychotic medication is usually the gold standard in treating schizophrenia. This treatment usually exist in some form of combination with additional required neuroleptics (if needed) and in some combination with an in- or- outpatient- program.

All modalities will usually also include a form of psychotherapy in combination with traditional psychotherapy and/or cognitive (behavioral) therapy. ²⁾ According to several studies, this combination of medical treatment and psychotherapy/CBT has shown to be the most effective in preventing relapses ^{3), 4)}

Probable pitfalls in any study conducted on this topic include:

Patients with schizophrenia and related psychotic disorders may be admitted for a vast variety of reasons; this may in some cases jeopardize the study because different criteria of success of outcome will be used.

Failure to comply with treatment in both control groups and intervention groups may be a frequent obstacle in studies done in psychiatric patients.

In studies not primarily intended to research drug- regimens, but rather different types of psychotherapy/CBT or alike, the drugs used concurrently in different patients may not be the same. This may be because the optimal effect of anti- psychotics is often individual ²⁾, and thus the drug giving the best response is often used, also during conducting studies.

To prevent that these potentially extensive and expensive treatments be futile, it is imperative to have a proper follow- up program and a structured plan for the patient after release from institution.

We have several different possibilities in choosing which program to use, all varying in cost- effectiveness, success- rate in the prevention of relapses and several other aspects. Different countries will apply different methods according to their resources, but also according to their different politico- medical stand- point and research applied.

An overview of the most common challenges in preventing relapse and the commonly employed methods concerning this topic will follow. Relapse symptoms will be explained and the different strategies mostly employed in preventing them will be explored. Also, it will be discussed which factors that should be considered in association with relapse. The effectiveness of the different approaches will then be discussed in further detail.

IDENTIFYING RELAPSE SYMPTOMS:

There is strong evidence that relapse is preceded by early signs. It is also a well known notion that early detection of symptoms and thus early intervention is crucial to prevent further deterioration and re- admissions ^{2) 3) 8) 27)}.

One of several challenges in identifying and treating relapse symptoms is the heterogeneity of symptoms; they differ in duration, intensity, number and speed of onset between patients; e.g. (di)stress is a well- known trigger of psychotic symptoms and relapse. The distress may be provoked by some of the symptoms of schizophrenia and psychosis itself (e.g. hallucinations, thought disturbance, withdrawal), thus creating a vicious deteriorating spiral ^{8) 10)}.

Retrospective and prospective studies of relapse symptoms

An interview study by Herz and Melville (1980) from USA attempted to systematically collect data retrospectively from patients and relatives on their experience of early signs of relapse. 145 patients with schizophrenia and 80 of their family members. Both groups were asked if they could remember any changes in thoughts, behavior or feelings that led the patient to believe he/she needed hospitalization. 70% of patients and 93% of families answered «yes» to this question.

This result was backed up in a later British study (Birchwood et al., 1989). The most frequent symptoms were eating less, concentration problems, trouble sleeping, depressed mood, and withdrawal. The most common “early psychotic” symptoms were auditory hallucination with voices, talking in a nonsensical way, increased religious thinking, and thinking someone else was controlling the patient ⁽⁸⁾. The same studies also inquired about the timing of the onset of the prodromal symptoms;

Most of the patients (52%) and their families (68%) in the Herz and Melville study said that more than a week elapsed between the onset of the prodrome and a full relapse; Birchwood et al. (1989) found that 59% observed the onset of the prodrome one month or more prior to relapse, and 75% two weeks or more; 19% were unable to specify a time scale ⁽⁸⁾.

Several studies have been done to determine especially alarming and less alarming symptoms, and their prediction for relapse; so- called prospective studies ⁽⁹⁾, table 1.

The symptoms often observed in prodromes before relapses were more or less concurrent with each other in these 9 studies ⁽⁹⁾.

- Marder et al., Sobotnik & Neuchterlein, Hirsch & Jolly and Malla & Norman all found that symptoms of depressed mood, thought disturbance and paranoia almost always were present in prodromal phase before relapse.
- Marder et al. however, also concluded that the observable degree of deterioration in symptoms were very small, and probably not detectable by most physicians. This will probably lead to many false positives in a clinical setting if applied.
- Sobotnik & Neuchterlein also found that many patients did not have any symptoms until 2-4 weeks before relapse, and some did not have any symptoms.
- Malla and Norman found that minor fluctuations in psychotic symptoms were not significant enough to cause dysphoria 1 month later, but the opposite was true in severe worsening of psychotic symptoms.

Table 1 – *Prospective studies of the Predictive Power of “Early Signs”*

Authors	N	Classification	Assesment of early signs	Relapsers	Sensitivity	Specificity	False positives
Marder et al. (1984)	41	DSM-3R	BPRS	42	48	?	?
Subotnik and Neachterlein (1988)	50	RDG	BPRS	25	59	7	26
Birchwood et al. (1989)	19	PSE-9	Early Signs Scale (ESS)	8	63	82	11
Hirsch and Jolley (1989)	54	DSM-3	Early sign questionnaire, SCL-90	10	73	?	?
Marder et al. (1991)	50	DSM 3-R	BPRS, individualized programme scale	18	50	?	20
Tarrier et al. (1991)	84	PSE-9	Psychaitric assesment scale (PSA)	16	50	81	?
Gaebel et al. (1993; 2000)	364	ICD-9 RDG	BPRS	162	8	90	?
Maila and Norman (1994)	55	DSMS-R	Beck Depression Inventory (BDI)	16	50	90	?
Jorgensen (1998)	60	ICD-10	ESS	27	74	79	26

BPRS= Brief Psychiatric Rating Scale (Overall & Grahan, 1962)

SCL90= self- report measure of symptoms (Derogatis, Lipman & Covi, 1973)

Source: M. Birchwood and E. Spencer

Different methods were applied (table 1), and the result were often in accord with each other; many of the same symptoms were reported to be a part of the prodromal period before finally a relapse occurred.

Several other studies confirmed that patients (in addition to caregivers) often are able to identify prodromal symptoms themselves²⁷⁾.

From a **prospective** point of view it is also interesting the many potential risk factors mentioned in a vast number of literatures. There is, however, not clear how big role the different risk factors play in the development of schizophrenia.

From a genetic point of view, especially the rare velo- cardio- facial syndrome (VCFS - associated with microdeletion of chromosome 22q11) is interesting. Patients with this syndrome have a lifetime prevalence of schizophrenia 25 times higher than that of the general population ¹⁶⁾.

From a biological/neuropsychological point of view, there are several biological markers suspected of having some impact on the development and recurrence of schizophrenia; Structural brain pathology ^{17a, b, c)} (e.g. larger 3rd ventricles, decreased hippocampus and gray matter), minor physical anomalies like dermatoglyphic abnormalities ^{18, 19, 20)} and increased electrophysiological latency ²¹⁾ may all contribute to increased risk of relapse.

Some other risk factors which may also contribute to the development of and thus also may increase the relapse of schizophrenia are family history of schizophrenia (45- 50% concordance in monozygotic twins, 10- 15% in dizygotic twins), low maternal vit. D or maternal infection during pregnancy, and stressful environment ¹⁷⁾.

Important factors that should be considered in association with the duration of treatment and risk of relapses are many and still a topic subjected to debate and vigorous investigation.

One of the most recognized factors is the time it takes from the onset of symptoms to the actual initiation of treatment; that be if it is the first psychotic episode or in a patient with long-standing schizophrenia ²²⁾. At least 10 studies done on different continents found that average time it took from initiation of symptom to treatment was initiated, bordered on 1-2 years ²²⁾. A Dutch Cohort study over 15 years, including 182 first- contact schizophrenic patients concluded that early intervention strategy could prevent further damage and deterioration ²⁶⁾.

A recent and somewhat controversial hypothesis, suggests that *prolonged psychosis* may actually be neurotoxic. This means that actual brain damage may occur and may contribute to prolongation of symptoms, treatment resistance or increased risk of relapse of symptoms. This is hypothesized by two studies and meta-studies ^{23) 31) 32)}.

Interventions employed to prevent relapses

The measures to prevent relapses after treatment are many. The ones that are mostly used will be discussed in the next sections.

OUTPATIENT TREATMENT

The outpatient part of treatment in schizophrenia and related psychotic disorders is an imperative cornerstone after hospital discharge. The importance of some outpatient programs will be also be substantiated in the below discussion on Relapse Prevention Plans and medication use.

There are many different versions of outpatient programs, depending on country and also regions within countries, and usually a mix of the below discussed programs exists. However, there are more similarities than differences in the various programs, and all modalities employed should be based on clinical evidence. Because of the importance of detecting relapse symptoms rapidly and to enable quick response, several countries also have outpatient programs without consent of the patient, trying to ensure maximal compliance.

A problem with studying the outpatient programs is that since there is no standardized way to structure plans or to intervene, comparability of trials/studies are decreased. Treatment as usual/standard care in these studies translates to hospital- based treatments.

Examples and evaluation of the most commonly employed outpatient programs will be discussed in the next section.

INTERFACE BETWEEN PRIMARY AND SECONDARY CARE⁵⁴⁾

It should be distinguished between first episode schizophrenia and people with an established diagnosis and a long history of the disease.

The first group should be referred to secondary care (specialist in psychiatry) as soon as possible for further diagnostics.

The second group of patients have often been treated in special psychiatric hospitals/centers, and have then been discharged, to be followed up by community GP or alike. Here, it is important that the GP has regular evaluations of mental state, side effects of medications, compliance, social status and physical status. Carers may also be included. It is extremely important with proper communication

between different levels of the health system (primary and secondary), as this has been shown to keep patients stable and well functioning ⁵⁴⁾.

COMMUNITY MENTAL HEALTH TEAMS (CMHT) ⁵⁵⁾

One of the first ways of organizing outpatient care (Merson et. Al, 1992) was the use of CMHT's; many disciplines comprising nursing, occupational therapy, psychiatry, psychology and social work are combined to provide the best care. It is now the main- stay of treatment in developed countries and is what many newer treatment options are compared to in studies and trials (Pierides, 1994; Slade *et al*, 1995; Isaac, 1996) ⁵⁵⁾, often referred to as “treatment as usual.” 4 studies on CMHT treatment conclude that even this is still the mainstay community mental health care, there is surprisingly little evidence to show that they are an effective way of organizing services. Thus, evidence for or against the effectiveness of CMHTs in the management of schizophrenia is insufficient to make any evidence-based recommendations ⁵⁵⁾.

ASSERTIVE (COMMUNITY) OUTREACH PROGRAMS ⁵⁶⁾

Developed in the 1970's, this program was designed to provide treatment and care for serious mental health problems *in the community*. The aims are to keep the seriously mental ill patient in contact with health- care providers, to decrease admissions and to improve outcomes after discharge. A multi- disciplinary team is usually involved and patient groups included are usually strictly defined. Even though most of the studies done on this type of program has been done in the U.S., the results may at least to some extent be valid in Western European countries as well; Several studies concluded that there is evidence that for patients with severe mental disorder, an Assertive outreach programs is more likely to fulfill the goals mentioned above, than if they follow CMHT ⁵⁶⁾.

ACUTE VS. NON- ACUTE DAY HOSPITAL CARE ⁵⁷⁾

Acute day hospitals may be compared to the emergency room in somatic hospitals; This modality is for patients who would otherwise be admitted to in- patient treatment. If eligible, patients may be treated acutely, without the need for admission to a long- term facility. Results of studies done on this type of treatment show that it substantially reduces the hospital bed use without adversely affecting family, recovery rate and social functioning ⁵⁷⁾.

The evidence for the effectiveness of *non-acute* day hospital (with continuing care) in improving clinical outcomes for people with severe mental illness has been disputed (Hoge *et al.*, 1992), and some even think such centers may even be doing harm than good to patients or the family/friends (Tantam & McGrath, 1989). Studies show that it offers no advantage over standard outpatient care for patients have responded badly to standard care ⁵⁷⁾.

CRISIS RESOLUTION AND HOME TREATMENT TEAMS (CRHTT) ⁵⁸⁾

Any type of crisis- oriented treatment of acute psychiatric episode by staff trained to deal with those situations. Treatment is provided also outside office hours.

Although studies showed that CRHTT decreased likelihood of being admitted while being followed up by the program, and also lead to shorter admissions, it has not been proved that it changes the chance of being readmitted, when comparing to standard care. However, studies concluded with that CRHTT is superior to standard care, and also seems to be more acceptable to patients ⁵⁸⁾.

ENVIRONMENTAL FOCUS

Environmental focus in prevention of relapse has gained more territory the recent years. The importance of information about schizophrenia/psychosis to carers and family, but also to the general public has been emphasized. Strategies have been implemented in several countries (Norway and UK among others ²⁴⁾), the goal being to decrease the public's social stigmata towards psychiatric diseases.

There have also been employed several types of *social skill training* programs over the years, showing little evidence of it's benefit. However, this result is based upon mostly one study with many methodological problems ⁵⁴⁾.

Substance abuse has become a bigger problem the recent years in associations with relapse ^{54 b)}, prevalence and its clinical and social effects (Banerjee *et al.*, 2002). Monitoring drug and alcohol abuse is thus an essential aspect of the management of people with schizophrenia in primary and secondary care ⁵⁴⁾.

RELAPSE PREVENTION PLANS

Relapse prevention plans (RPPs); Any concrete plan (written or oral) specifically designed to discover relapse symptoms and then how to intervene.

RPPs will usually be present in some form in most of the countries with a developed health/psychiatry- system and will thus be one of the topics discussed most broadly in this article. The ITAREPS program will also be discussed in this section.

Since there are many different ways to employ an RPP in practice (frequency of follow- ups, availability of trained personnel and control of compliance of the patients), it is important to determine the exact methods used in any trial or study ⁵⁾. This so ensure that the actual study can be transferred and used correctly in a program of relapse prevention.

One study ³⁾ performed with 48 patients (22 in control group, 26 in experimental group), showed no significant difference between conventional treatment and experimental relapse prevention plan (RPP) after 1 year follow- up; Relapse rates were 26,2% and 12,5% respectively, $p= 0,12$.

The study does not state what is included in “conventional treatment”.

The experimental RPP of the study included four successive phases;

- 1) Preparatory; information and education about psychosis and schizophrenia to patient and patient's social network. A systematic assessment of factors that can promote/hinder relapse was done.
- 2) Early potential signs were systemically inventoried and classified as normal/stable, light/moderate or severe.
- 3) Monitoring phase; patient and involved persons was informed on how to score in 2)
- 4) An action plan was prepared: managing stress, enhance coping, protection from surroundings.

The study concluded with that more studies with substantially larger sample size and longer follow- up periods should be conducted to make these relapse rates statistically significant.

Other studies worth mentioning concerning relapse in association with RPPs include:

Herz et al. (2000): They standardized the medication administration and examined the effects of a program for relapse prevention. They compared this intervention program with a control condition in which care as usual was offered. Active monitoring of early signs was combined with psychoeducation and weekly group therapy for patients and family meetings.

After 18 months, they found *significant differences* between the two groups in psychotic relapses and rehospitalizations. ⁶⁾

Another study ⁷⁾ observed the effects of Libermann Modules (group therapy oriented to various skill areas in combination with providing knowledge and training in recognizing symptoms). The “Symptom Management” module is directed to early recognition of psychotic relapse. The effect on re- hospitalizations was studied, and the conclusion was that the training had no significant effect on the number of readmissions, but *did* have an effect on their duration.

Another type of RPP has been described in *Psychiatria Danubina, 2006; Vol. 18, No. 1–2, pp 61–73* ²⁵⁾. In this study from Croatia, also Bipolar Affective Disorder (BAD) is exemplified as a disease that may also be controlled better with similar RPPs like in schizophrenia/related psychotic disorders. Relapse of BAD into manic phase is often connected with increased energy, creativity and goal- directed activities, while relapse into depressive phase is connected with symptoms of milder depression ²⁵⁾. In this study they describe several systems in which warning signs are established and described in the patient's own words or using standardized well- known symptoms of relapse, referred to as «relapse signatures». Then, an agreement of an action- plan following those relapse symptoms is signed by all parties involved (also caregivers). Cards are then made with the signature symptoms and placed by the patient on a drawn time-line on a sheet of paper.

The conclusion made by the authors of this article was that after doing this exercise, patients were able in a much higher degree to establish a longer time- line of symptoms leading to a relapse. This, in turn, made it possible for caregivers/treatment teams to intervene earlier and thus more often prevent re- admissions/relapses ²⁵⁾; Number of relapses went from 1 pr. year – 1 pr. 3 years to 0 in all the patients tested (table 2). This result was apparent in schizophrenia, schizo- affective disorder and BAD. The apparent limitation of this approach is that patients need at least one relapse before the program can be used, this to be able to identify symptoms “specific” for that patient.

Table 2: Results of a pilot study of the use of early warning signs to reduce the relapse rate of patients with psychotic illness.

Patient	Diagnosis	Number of relapses Before Signature Done	Expected Relapse rate	Date early signs done [months since signature done]	Admissions since early signs done
34	mania	3	1/2years	10/01 [14]	0
38	schizophrenia	0	0	2/02 [9]	0
1	schizophrenia	5	1/2years	12/01 [11]	0
33	schizophrenia	1	1/3years	10/01 [13]	0
43	schizophrenia	6	1/year	10/02 [2]	0
3	psychotic depression	1	1/year	2/02 [9]	0
15	schizophrenia	1	1/2years	2/02 [9]	0
16	schizophrenia	2	1/year	8/01 [15]	0
21	schizophrenia	2	1/year	7/01 [16]	0
32	schizophrenia	3	3/year	1/02 [10]	0
11	schizophrenia	2	1/2years	7/02 [5]	0

Source: Mark Agius, Hilary Oakham, Sanja Martić Biočina & Suzanne Murphy: *The use of card sort exercises in the prevention of relapse in serious mental illness; Psychiatria Danubina, 2006; Vol. 18, No.1–2, pp 61–73*

In England, the UK Government has committed itself to developing Early Intervention Services across the country³⁴⁾, as part of The National Health Service plan (2001); teams stationed all around the country follow patients especially close for 3 years, ready to intervene if necessary.

This builds on the notion that there exists two important concepts associated with deterioration; «critical period» and «duration of untreated psychosis.»

The critical period was described and hypothesized by Prof. Max Birchwood in 1998; there is often major change in psychosocial functioning of many people with schizophreniform illnesses within the first 3 years of onset, then the deterioration flattens out. Thus, according to this concept, the patients should be treated aggressively the first 3 years to improve the long- term outcome³⁴⁾.

Duration of Untreated Psychosis (DUP) is, according to De Haan (2003), also important because a long DUP shortens the time available to initiate treatment in the critical period³⁴⁾.

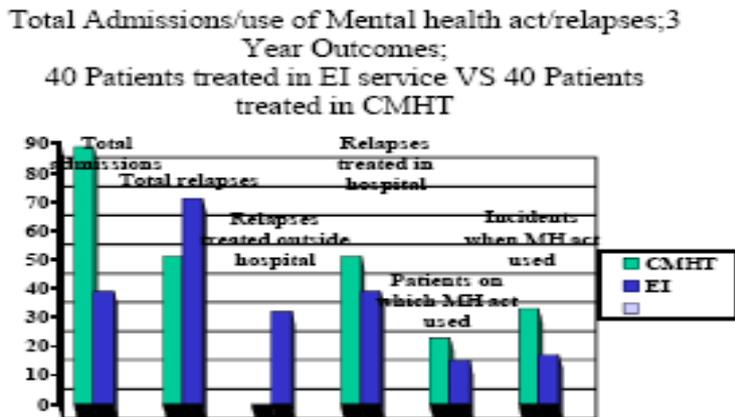
One study³⁵⁾ implementing this system in a psychiatric hospital in Luton, testing 3- year outcomes, showed that patients on this Early Intervention plan were (compared to control group with treatment as usual):

- more likely to take medication at the end of the three- year period (higher compliance)
- more likely to be prescribed atypical antipsychotics
- more likely to have returned to work or education
- more likely to be living with their families
- less likely to suffer depressions requiring anti- depressants.
- less likely to attempt suicide
- less likely to relapse and re- hospitalize, less likely to have involuntary admissions (see fig. 1)
- More likely to have stopped illicit drug use (not statistically significant in this test, probably because of too small sample size)

- receiving more psychoeducation

All changes (unless otherwise stated) were found to be statistically significant.

Fig 1: From *Three year outcomes of an early intervention for psychosis service, as compared with treatment as usual for first psychotic episodes in a standard community mental health team; Preliminary Results Psychiatria Danubina, 2007; Vol. 19, No. 1-2, pp 1.* ³⁵⁾



CMHT= Community mental Health Team (treatment as usual)

EI= Early Intervention plan

A follow- up study with a larger group of patients (62, compared to 45 in the first study) confirmed the above findings, and also an additional finding that EI patients managed relapses better than the CMHT patients, was discovered ³⁶⁾.

When it comes to RPP's there are, as stated above, many different variations, most of them aimed at detecting early symptoms of relapse as a mode of early intervention. In addition to the above mentioned systems/programs, the recently developed ITAREPS program will in the following section be discussed.

THE INFORMATION TECHNOLOGY AIDED RELAPSE PREVENTION PROGRAM IN SCHIZOPHRENIA (ITAREPS)

ITAREPS is another type of RPP which aims at using home telemonitoring via a phone- to- SMS platform ^{28) 29) 33)}. The program was developed at the Prague Psychiatric Center, Czech Republic in 2005 by F. Španiel et. al.

Weekly updates via this system from patients to health professionals are provided by evaluating prodromal symptoms of relapse and thus prevent hospitalization. The preventive measures of the program aims at interventions which has proved effective in preventing relapses;

Almost real- time review of the patient's mental status (Herz et. Al, 2000), increase anti- psychotic medication or provide additional support from health- care providers or caregivers (Fitzgerald, 2001) ²⁹⁾.

Patients enrolled in the program complete a 10- step Early Warning Sign Questionnaire (EWSQ) via SMS, once a week. Another set of questionnaire may be answered by family members. No special training is needed for any of the participants.

In contrast to the system described above (*Psychiatria Danubina, 2006*) with «relapse signatures», the ITAREPS EWSQ contains 9 standardized questions concerning the most common non- specific warning signs, and 1 question concerning three specific symptoms which individually has preceded previous relapses. The steps are scored by the patients/their carers from 0 (no change/improvement) to 4 (extreme worsening), see table 3 ²⁹⁾.

The score is sent to ITAREPS and automatically cross- referenced with a predefined threshold score. An «alert» is sent to the treating physician by e-mail if the threshold is exceeded, and (telephone) contact with the patient is achieved.

Immediate measures (within 24 h) is to increase the anti- psychotic medication with 20% (confirmed by Herz et. Al, 2000). Then, patient- doctor contact face-to-face is established.

The alert period continues for 3 weeks with 2 EWSQ/week, and if 6 subsequent EWSQ shows no deterioration, the anti- psychotic drugs are tapered. If not, the status is upgraded to «Alert emergency,» extending the «Alert period» for another 3 weeks. All the alert period steps are notified to the physician via email. Also, using the ITAREPS web- page (www.itareps.com), doctors may monitor admissions, outpatient visits, alerts, medications etc in a transparent lay-out ²⁹⁾.

Table 3: *Early warning signs questionnaire, patient and family member version*

Item no.	EWSQ 10 Patient Version	EWSQ 10 Family Member Version
1	Has your sleep worsened since the last evaluation?	Change of the sleep pattern.
2	Has your appetite decreased since the last evaluation?	Marked behavioral changes.
3	Has your concentration, e.g., ability to read or watch TV, worsened since the last evaluation?	Social withdrawal.
4	Have you experienced fear, suspiciousness, or other uneasy feelings while being around other people since the last evaluation?	Deterioration in daily activities and functioning.
5	Have you experienced increased restlessness, agitation, or irritability since the last evaluation?	Deterioration in personal hygiene.
6	Have you noticed that something unusual or strange is happening around you since the last evaluation?	Loss of initiative, motivation.
7	Have you experienced loss of energy or interest since the last evaluation?	Eccentric thought content, marked preoccupation with strange ideas.
8	Has your capability to cope with everyday problems worsened since the last evaluation?	Marked poverty of speech and content of thoughts.
9	Have you experienced hearing other people's voices even when nobody was around since the last evaluation?	Irritability, restlessness, agitation, aggressivity
10	Have you noticed any other of your individual early warning signs since the last evaluation?	Have you noticed any other individual early warning signs since the last evaluation?

Source: Španiel, F. et al., ITAREPS: Information Technology Aided Relapse Prevention Programme in Schizophrenia, Schizophr. Res. (2007), doi:10.1016/j.schres.2007.09.005.

Two subsequent clinical trials (2007 and 2008) have been conducted by the creators of the ITAREPS^{28) 30)}. Both were done on patients with diagnosis of schizophrenia, schizoaffective disorder or polymorphic psychotic disorders, using diagnostic criteria from ICD-10.

The first clinical evaluation (2007) ³⁰⁾ followed 45 patients and 39 family members over 283,3 ± 111.9 days. 88 cases of «Alert periods» were initiated by patients, and 47 by family members. Drop-out was 10%. The result of this study was a decrease of statistically significant 60% in no. of hospitalizations during the program (from 27 to 9, $p < 0,004$, pre-set statistical significance $p \leq 0,05$). In highly cooperative patients, the same no. was 100% (from 13 to 0).

The 2 year follow- up study (2008) showed a decrease in no. of hospitalizations of 77% and a decreased no. of hospitalization days; from 2365 days to 991 days (58%), during ITAREPS. The trends from the first study were all confirmed by this follow- up study. The conclusion was that ITAREPS is an effective tool in the long- term treatment of patients with psychotic disorders ²⁸⁾.

ITAREPS has in the later years been employed in a number of different countries around the world; Slovakia, Japan, Netherlands, Great Britain, Saudi Arabia, Algeria, Malaysia and Taiwan. Extensive studies are yet to be done in these countries about the prevention of relapse, but similar results as in Czech Republic should be expected.

In terms of cost- effectiveness, the ITAREPS program and result of studies show a potentially great reduction in health costs of schizophrenia ³⁷⁾; Without ITAREPS employed, the cost pr. relapse in Czech Republic is about 4950 Euro, but potentially 1970 Euro (using the assumption of 60% time cumulative hospitalization reduction) using the ITAREPS system. However, further analysis concerning cost- effectiveness must be done ³⁷⁾.

A quotation from the «full summary version of NICE's (National Institute of Health and Clinical Excellence, UK) guidelines to schizophrenia (Latest review march 2009) will summarize the section on Relapse Preventon Plans; «There is consistent evidence at 18-24 month follow- up that Early Intervention services when compared with standard care, produced clinically significant benefits for a number of critical outcomes including relapse, rehospitalization, symptom severity, satisfaction and quality of life. However, there is currently insufficient evidence to determine whether these effects are sustained past 2 years, with one RCT (N = 547) failing to find consistent evidence of benefit at 5 years follow-up ⁵³⁾. »

COGNITIVE BEHAVIORAL THERAPY (CBT) AND TRADITIONAL PSYCHOTHERAPY

CBT has, especially in recent years, grown to be more or less a standard mode of treatment in psychiatry and psychology ¹¹⁾. It is used both as a stand-alone treatment in an outpatient- setting as well as in various in- patient clinical settings ¹²⁾¹³⁾. CBT has been proved by several studies to be effective in treating at least some cases of some common psychiatric illnesses; Anxiety, personality disorders, eating disorders, substance abuse and some cases of psychosis. ¹²⁾¹³⁾.

Because CBT used correctly potentially can be very effective, and may also be used in shorter (outpatient) sessions, several studies have explored the importance and usefulness of this treatment in preventing relapses in schizophrenia.

One UK study in British Medical Journal, Evidence Based Mental Health, abstracted from Garety PA, Fowler DG, Freeman D, et al. ¹⁴⁾, asked the question; «What effect does CBT/family therapy have in the prevention of relapses in schizophrenia?»

Relapse was defined as «re-emergence of, or significant deterioration in, positive psychotic symptoms of at least moderate severity, persisting for ≥ 2 weeks.»

301 patients participated in this single- blind study; 218 with carers, 83 without; all were randomly allocated to CBT (12-20 sessions over 9 months) or treatment as usual (TAU). Follow- up was 24 months.

The conclusion was that «neither CBT nor family therapy improve relapse rates or reduces the number of days in hospital for people with psychosis who have recently relapsed.»

Another interesting additional finding in this study was that relapse rates were higher (37-55%) in patients living alone than in patients with carers (21-28%).

The authors of the study proposes, however, that CBT may give some modest benefits in individual cases, but then with concurrent treatment with proper medication. This is because CBT may reduce emotional stress, which is a known trigger of psychosis in many cases ¹⁵⁾.

The above study is in slight contrast to a 2003 study from Glasgow, that concludes with the following in comparing CBT with treatment as usual (TAU): “There is evidence for the feasibility and effectiveness for targeting CBT on the appearance of early signs of relapse in schizophrenia.» The relapse was apparent in 13 patients of the CBT group and 25 in the TAU gr. and re- hospitalization occurred in 11 of CBT patients vs. 19 in TAU gr. ⁴⁰⁾.

One randomized controlled study (422 people with chronic schizophrenia) compared CBT given by mental- health nurses plus standard care vs. usual care *alone*. It found that nurse-led CBT significantly reduced relapse rates compared with usual care at 12 months' follow-up (14% in CBT groups vs. 24% in the care as usual group, $p < 0.05$). The nurses were intensively trained in CBT techniques, however, and were not from community- health teams ³⁸⁾.

Several studies have been conducted on the use of CBT in preventing relapses in schizophrenia and related psychotic disorders. The results of the studies have often been inconclusive or shown a small benefit of CBT (like proposed in the above mentioned study) when compared to traditional psychotherapy ^{38) 39) 40) 41)}.

A big review done by NICE guidelines (National Institute of health and Clinical Excellence, U.K.) in 2009 found that consistent evidence exists that when compared to standard care, CBT was according to the studies analyzed *effective in reducing rehospitalization rates up to 18 months following the end of treatment*.

Additionally, there was robust evidence indicating that the duration of hospitalization was also reduced (8.26 days on average). Consistent with previous NICE guideline reviews, CBT was shown to be effective in reducing symptom severity as measured by PANSS (Positive And Negative Syndrome Scale) and BPRS (Brief Psychiatric Rating Scale), both at end of treatment and at up to 12 months follow-up.

Other interesting conclusions reached by this review, but not concerning primary relapse prevention was that small to medium effects (SMD ~0.30) also demonstrated reductions in depression when comparing CBT to both standard care and other active treatments.

Furthermore, when compared to any control, there was some evidence for improvements in social functioning up to 12 months.

Although the evidence for positive symptoms was more limited, analysis of PSYRATS data showed some effect for decreasing hallucinations at the end of treatment. Also, there was some limited but consistent evidence for symptom specific measures including voice compliance, frequency of voices and believability, all of which demonstrated large effect at both end of treatment and follow-up.

However, despite these positive effects for hallucination-specific measures, the evidence for there being any effect on delusions was inconsistent ⁶⁰⁾.

MEDICATIONS USED IN RELAPSE PREVENTION

[A detailed description of different antipsychotics and their side-effects, doses etc. is beyond the scope of this article].

Stopping antipsychotic medication in people with schizophrenia, especially if done abruptly, dramatically increases the risk of relapse in the short to medium term, although even with gradual cessation, about ½ will relapse in the succeeding 6 months (Viguera *et al.*, 1997). Low-dose prescribing and the use of intermittent dosing strategies (with medication only when early signs of relapse occurs) have also been suggested in the past as ways to minimize side effects long-term. However, when these were tested in controlled trials, the risks, particularly in terms of increased relapse, outweighed any benefits (Dixon *et al.*, 1995; Hirsch & Barnes, 1995)^{54b}.

It has thus been shown in several studies that maintaining a stable supply of proper neuroleptic medication and dosing after discharge is crucial to prevent relapses, better than short intermittent periods of medication^{2) 25) 43)}. For people with established schizophrenia, the chance of relapse when receiving continuous antipsychotic medication appears to be about a third of that of placebo (Marder & Wirshing, 2003). At least 4 studies introduced the concept that increasing medication when the prodromal symptoms of relapse were developing was a useful way of reducing the risk of relapse (Jolley *et al.* 1989 & 1990, Carpenter *et al.* 1990, Marder *et al.* 1994).

Regarding the importance of stable medications, compliance is thus of crucial importance in preventing relapses⁴⁴⁾; Patients who experience less side-effects and get motivational support on an outpatient-basis, show a bigger compliance than patients who have a higher side-effect profile and get little support⁴⁴⁾.

Conventional antipsychotic drugs such as chlorpromazine and haloperidol were introduced in the 1950s and are effective in treating acute psychotic symptoms and in preventing relapse^{45) 46)}. The prevention of relapse, however, requires long and even sometimes lifelong therapy, giving high rates of extrapyramidal side effects; tardive dyskinesia occurs in about 5 percent of patients after 1 year of treatment.

This means that, in order for the regimen to be accepted by patients, drugs must be effective, safe and have a low side-effect profile. Since compliance is the main factor limiting the use of the typical antipsychotics, newer (atypical) drugs are nowadays more frequently being used⁴⁷⁾.

In comparing different medications used in an outpatient setting, it is important to consider as many aspects of the treatment as possible to make sure the compliance remains as high as possible; side-

effect profiles, additional monitoring needed, the form in which the drug is taken (usually PO or IM) and previous experience with antipsychotics in that patient.

Several studies show that the atypical PO Clozapine (lower D2- receptor affinity) is superior to almost all other PO alternatives both in terms of effectiveness and side- effect profile. However, potentially severe agranulocytosis may develop (0,8 % /year), and (costly) blood- monitoring is imperative. This may again lead to less compliance of the patient because he/she has to continue blood- monitoring on an outpatient basis to continue taking Clozapine ⁴⁴⁾.

Medications that can be injected would substantially increase the compliance in many patients, as the drug is administered by health- care professional usually once or twice pr. month. There are not many forms of IM antipsychotics on the market today; Risperidone being by far the mostly used ⁵¹⁾.

A trial comparing the typical IM Haloperidol to the atypical IM Risperidone over 1 year, showed that patients using Risperidone had *substantially* lower relapse rates (34 %) compared to the Haloperidol group (60 %), $p < 0,001$ ⁴⁸⁾.

A new version of Olanzapine (Olanzapine pamoate/ZypAdhera) was approved for use in 2008/2009 ⁵⁰⁾. This IM version of Olanzapine aims at increasing the compliance of this drug, which is one of the most widely prescribed antipsychotic medications today ⁵¹⁾.

A 3- year trial that finished sept 2009, conducted by Eli Lilly and Company, set out to compare the PO Olanzapine with IM Olanzapine in respect to relapse, but as of p.t., no results have yet been published.

A current phase 3- study (as of sept. 18 2009) with the new atypical antipsychotic Asenapine (Trade- name Saphris/Sycrest [Europe], in development by Schering-Plough) has showed promising results in terms of relapse prevention; 12% relapse in Asenapine group in contrast to 47% relapse in placebo group ⁴⁹⁾. The drug is the first psychotropic drug to be administered sublingually. This may, according to the researches, increase the compliance ⁴⁹⁾. The drug has also been approved for acute episodes of mania.

Recent pharmaceutical research in psychiatry has relied very much upon funding from the private pharmaceutical industry. It is thus important that further independent studies on this matter be conducted, to ensure evidence- based information ⁴⁴⁾;

One big U.S. government- funded study that began May 2006 and is scheduled to be completed Dec. 2010, sets out to compare IM forms of antipsychotics (long- acting Risperidone) to PO atypical antipsychotics in the prevention of relapse in schizophrenic and schizoaffective patients ⁴³⁾.

Summary

It has in this review article been cited several different studies and sources, all concerning the prevention of relapse of schizophrenia and related psychotic disorders; The different approaches to treatment (programs, type of psychotherapy etc.) have been discussed according to evidence- based research and randomized controlled trials. Although some explanations have been given about terms used in the literature, as well as some definitions to enable classifications in future studies, it has been focused only on the preventive measures used in schizophrenia; a detailed description of different subgroups of schizophrenia, as well as detailed descriptions of pharmacology in neuroleptics is beyond the scope of this article.

The recognition of relapse symptoms was first considered and defined, and the different approaches was then discussed;

Outpatient treatment plans and relapse prevention plans, as well as the impact of cognitive behavioral therapy and psychotherapy have been discussed in subsequent chapters. In this section, it was especially focused on the ITAREPS program and its impact on the relapse prevention. The role of medications was then defined and supported with clinical studies and trials.

Conclusion

It is clear from the research that have been done on the topic that problems concerning standardization poses a big challenge also in future studies; it is important to have standardized trials to best be able to compare them to others, and to best employ them in clinical practice.

In developed countries, there are various versions of “classic” relapse prevention programs in the form of patient outreach programs. Although this is vastly used, studies fail to confirm that this type of treatment alone will benefit the patient.

However, if combined with psychotherapy and/or cognitive behavioral therapy and psychoeducation, the rates of relapse usually decrease. When comparing CBT and traditional psychotherapy, CBT has traditionally not been shown to be more beneficial according to studies. However, several studies done in the recent years on CBT have concluded that this form of therapy is effective in preventing relapses, especially when combined with medications. There are not many studies that conclude with

a clear superiority of CBT compared to traditional psychotherapy. This may be because it is sometimes difficult to use absolutely standardized approaches in the trials.

Several programs which are currently used worldwide have shown to be beneficial; it seems that the mapping of patients symptoms and realization of the patient about which symptoms are prominent in a prodromal period is very effective in preventing relapses. Here, also outpatient- programs with stress and symptom management in the form CBT or other structured communication has been shown to have effect.

One of the most important factors in preventing relapse seems to be compliance; being compliant to both outpatient consultations and in the using of prescribed medications is according to all the studies and experiences crucial.

Compliance in taking medications is best ensured with either IM administered medications or by using treatment without consent when this is found to be suitable. The long- term administration of medications is also superior to intermittent/short- term usage in preventing relapse.

From the health- care provider's point of view, studies show that early intervention programs are also a very important tool; by detecting early prodromal symptoms by means of different outreach programs like ITAREPS, the rate of relapse can be substantially reduced, sometimes even drastically.

Even though several studies have been done in the last years, further research need to be done on the topic of relapse prevention to ensure patients the newest and the best treatment.

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