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Biomarkers of Suicide Risk in Psychosis

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Egentligen vet man blott när man vet litet.
Med vetandet växer tvivlet.

Johann Wolfgang von Goethe

Go thy way, eat thy bread with joy, and drink thy wine with a merry heart; for God now accepteth thy works.

The Preacher, 9:7

ABSTRACT

Suicide and attempted suicide are major health problems. Approximately 1400 people die from suicide every year in Sweden and ten times more attempt suicide. Patients with schizophrenia spectrum psychosis have an increased risk of suicide and suicide rates have been suggested to be as high as 10%. Important risk factors include a prior suicide attempt and depressive disorder. Low concentrations of monoamine metabolites in cerebrospinal fluid (CSF) have been related to suicidal behavior in patients diagnosed with mood disorders. Few studies have investigated patients with schizophrenia spectrum psychosis and they suffer from small numbers of patients, short periods of follow-up and contradictory results.

The main objective of this study was to investigate the long-term suicide risk in schizophrenia spectrum psychosis, whether concentrations of the CSF monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) are related to suicidal behavior and to the overall mortality. The importance of other factors influencing suicide risk such as a prior suicide attempt, gender and CSF kynurenic acid (KYNA) was also investigated.

Inpatients (n=385) with schizophrenia like symptoms were lumbar punctured at admittance and followed up for a median period of 26 years. Information about prior suicide attempts was retrieved from the medical records. Causes of death were obtained from the Causes of Death Register.

During the follow-up period nearly equal percentages of men (6.5 %) and women (6.9 %) died by suicide. Eighteen percent of suicide attempters and 2% of the non-attempters died by suicide. The suicide risk was almost three times higher in male attempters than in females. Thus, attempted suicide and male gender were significant risk factors for suicide. There were neither any associations between CSF concentrations of 5-HIAA and HVA, or their ratio, nor between CSF KYNA concentrations and suicide or attempted suicide. CSF 5-HIAA and HVA concentrations were not a risk factor for early death from natural causes.

Patients with schizophrenia spectrum psychosis have a high long-term risk of suicide. Attempted suicide was a very important risk factor for suicide in both genders, especially in males. In contrast to patients diagnosed with mood disorders, CSF 5-HIAA and HVA concentrations were not associated with suicidal behavior in schizophrenia spectrum psychosis patients.

Keywords: gender, CSF, 5-HIAA, HVA, psychosis, survival, schizophrenia, suicide, suicide attempt, long-term follow-up, early death, KYNA.

LIST OF PUBLICATIONS

I. Long-term suicide risk in schizophrenia spectrum psychoses: survival analysis by gender.

Andreas Carlborg, Jussi Jokinen, Erik G. Jönsson, Anna-Lena Nordström and Peter Nordström

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II. Attempted suicide predicts suicide risk in schizophrenia spectrum psychosis.

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III. CSF 5-HIAA, attempted suicide and suicide risk in schizophrenia spectrum psychosis.

Andreas Carlborg, Jussi Jokinen, Anna-Lena Nordström, Erik G. Jönsson, Peter Nordström

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IV. Early death and CSF monoamine metabolites in schizophrenia spectrum psychosis.

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V. CSF kynurenic acid and suicide risk in schizophrenia spectrum psychosis.

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LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5HT	Serotonin
APA	American Psychiatric Association
CNS	Central nervous system
CSF	Cerebrospinal fluid
DSM-III	Diagnostic and Statistical Manual of Mental Disorders third edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision
HVA	Homovanillic acid
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases 10^{th} edition
KI	Karolinska Institutet
KYNA	Kynurenic acid
NASP	Sweden's and the Stockholm County Council's expert center for research into suicide and the prevention of mental ill-health
nM	One billionth (10-9) of a mole (nanomole)
NMDA	N-methyl-D-aspartate
NR	Not reported
NS	Not significant
Mole	A basic unit of amount of a substance
OR	Odds ratio
PCP	Phencyclidine
SD	Standard deviation
SMR	Standard mortality rate
SSRI	Selective serotonin re-uptake inhibitors
TCA	Tricyclic antidepressant
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

1.1 Schizophrenia

Schizophrenia and its related disorders affect approximately 1% of the population worldwide during a lifetime. Contrary to previous interpretations, the incidence and prevalence of schizophrenia shows marked variation between sites. For example, migrants have an increased incidence and prevalence of schizophrenia and exposures related to urbanicity, economic status, and latitude are also associated with various frequency measures ((McGrath et al., 2008). Men have a higher risk than women (Aleman et al., 2003) and a recent review concluded that men have a 40% higher incidence of schizophrenia than women ((McGrath, 2006).

Schizophrenia was previously called dementia praecox and the term schizophrenia was first coined by the Swiss psychiatrist Eugen Bleuler in 1908. Bleuler realized the condition was neither a dementia, nor did it always occur in young people (*praecox* meaning early) and so he gave the condition the less stigmatizing but still controversial name from the Greek roots *schizein* ("to split") and *phrēn* ("mind").With recent diagnostic refinements, psychosis (that is, a break with reality usually manifested as hallucinations, delusions, or a disruption in thought processes) has become central to the classification of schizophrenia.

Schizophrenia is a clinical syndrome characterized by symptoms of psychosis such as abnormalities in the perception or expression of reality. Distortions in perception may affect all five senses, including sight, hearing, taste, smell and touch, but this is manifested most frequently as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking with significant social or occupational dysfunction. The onset of the illness occurs relatively early in life, usually in the late teens or early adulthood, and most patients have long-lasting adverse effects. The personal tragedy associated with schizophrenia is extreme, since it attacks the human properties considered most precious and distinguishing (Carpenter and Buchanan, 1994).

Schizophrenia and its related disorders are diagnosed on the basis of symptom profiles. There are two main standardized criteria systems used to classify schizophrenia and its related disorders; the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM), version DSM-IV-TR, and the World Health Organization's (WHO) *International Statistical Classification of Diseases and Related Health Problems*, the ICD-10. The ICD-10 criteria are mostly used in the European countries while the DSM-IV-TR criteria are mostly used in the rest of the world and in research studies.

According to the revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* DSM-IV-TR, (APA, 2000), to be diagnosed with schizophrenia, three diagnostic criteria must be met:

1. **Characteristic symptoms**: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
    - Delusions
    - Hallucinations
    - Disorganized speech, which is a manifestation of formal thought disorder
    - Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior
    - Negative symptoms: affective flattening (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

    If the delusions are judged to be bizarre, or if hallucinations consist in hearing one voice participating in a running commentary on the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. **Social/occupational dysfunction**: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.

3. **Duration**: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

Schizophrenia cannot be diagnosed if symptoms of mood disorder or pervasive developmental disorder are present, or the symptoms are the direct result of a general medical condition or a substance, such as abuse of a drug or medication.

The DSM-IV-TR contains five subclassifications of schizophrenia (APA, 2000):

- **Paranoid type**: Where delusions and hallucinations are present but thought disorder, disorganized behavior, and affective flattening are absent. (DSM code 295.3/ICD code F20.0)
- **Disorganized type**: Named hebephrenic schizophrenia in the ICD. Where thought disorder and flat affect are present together. (DSM code 295.1/ICD code F20.1)
- **Catatonic type**: The subject may be almost immobile or exhibit agitated purposeless movement. Symptoms can include catatonic stupor and waxy flexibility. (DSM code 295.2/ICD code F20.2)
- **Undifferentiated type**: Psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. (DSM code 295.9/ICD code F20.3)

- **Residual type**: Where positive symptoms are present at a low intensity only. (DSM code 295.6/ICD code F20.5)

The ICD-10 (WHO, 1992) defines two additional subtypes.

- **Post-schizophrenic depression**: A depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present. (ICD code F20.4)
- **Simple schizophrenia**: Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes. (ICD code F20.6)

Many disorders may have symptoms of psychosis and the DSM-IV-TR lists 9 formal psychotic disorders. The formal psychotic disorders are:

1. Schizophrenia
2. Schizoaffective disorder
3. Schizophreniform disorder
4. Brief psychotic disorder
5. Delusional disorder
6. Shared psychotic disorder (Folie à deux)
7. Substance-induced psychosis
8. Psychosis due to a general medical condition
9. Psychosis - not otherwise specified

The exclusion of affective components from schizophrenia has resulted in a separate disorder, schizoaffective disorder in which symptoms of depression are included. Schizophreniform disorder is identical to schizophrenia except for the shorter duration of the disease and that impaired functioning is not required. A brief psychotic disorder lasts for less than one month. Delusional disorder involves holding one or more non-bizarre delusions in the absence of any other significant psychopathology (APA, 2000).

These psychotic disorders are often difficult to separate clinically, especially early on the course of illness. It is also common for diagnoses to change over time, especially in the patients with a long history of disease, and comorbidity with affective disorders and abuse of drugs and alcoholism is common making the diagnostic evaluation difficult. It is estimated that approximately 50% of all patients who at some time during their course of illness are diagnosed as schizophrenic are classified as something other than schizophrenic at their first admission (Munk-Jörgensen and Mortensen, 1992). The term schizophrenia spectrum psychosis is used in this thesis to describe the broader spectrum of psychotic disorders not only involving schizophrenia but also its related disorders described above.

Figure 1. Eugen Bleuler (1857–1939).

1.2 Etiology of Schizophrenia

Family, adoption and twin studies have shown that genetic factors play a major role in the development of schizophrenia and the liability to schizophrenia is highly heritable (about 60-80%). The concordance between identical twins is close to 50%, also suggesting the importance of environmental influences. Despite the genetic association the identification of specific genes has not been easy: linkage studies have identified a number of significant chromosomal regions, but hitherto no specific gene variant has been without doubt associated with the disorder (MacDonald and Schulz, 2009). The high heritability of schizophrenia may also be an effect of environmental influences that are moderated by genes, i.e. gene-environment interaction (van Os and Kapur, 2009). Several environmental factors increase the risk of schizophrenia and its related disorders. These factors include a history of obstetric complications such as asphyxia (Dalman et al., 2001) and prematurity (Ichiki et al., 2000). Advanced paternal age (Dalman and Allebeck, 2002) is also considered a risk factor and birth during the spring and late winter (Bradbury and Miller, 1985) also increases the risk. Prenatal viral infections (Barr et al., 1990), migrant status and urban rearing (McGrath et al., 2004) and a lifetime history of cannabis use (Sewell et al., 2009) are well-known risk factors.

1.3 Suicide and Suicidal Behavior

Suicide is defined as a self-inflicted death with evidence (either implicit or explicit) that the person intended to die. Suicide attempt is defined as self-injurious behavior with a non-fatal outcome accompanied by evidence (either implicit or explicit) that the person intended to die. Suicidal ideation is defined as thoughts serving the agents of one´s own death. These thoughts may vary in seriousness depending on the specificity of the suicidal plans and degree of suicidal intent (APA, 2003).

Suicide is among the leading causes of premature death in the world and it is estimated that approximately one million people die by suicide every year. Suicide rates vary according to region, gender, age, time, and ethnic origin, and also to death registration practices. The annual suicide rate in the world is 14.5/100000 (year 2000) which is equal to one suicide every 40^{th} second. Suicide is about three to four times more common in males than in females (WHO, 2008). Suicide rates vary between different

regions and underestimation of suicide rates is common due to underreporting, lack of epidemiological data and misclassification (Hawton and van Heeringen, 2009).

Countries with very high suicides rates include the Baltic states and the former Soviet republics with annual rates of up to 68/100000. Countries with low suicide rates include Latin American and Islamic countries with annual rates below 6.5/100000. There has been a general decline in the suicide rates in the world with an approximate decrease of 30% during the last 15 years (WHO, 2008).

In Sweden (2006) 1007 men and 451 women died by suicide corresponding to an annual rate of 19.5/100000. Suicide is the leading cause of death among those aged 15-44 in Sweden. The suicide rate in Sweden has decreased from 33.4/100000 in 1980 to 19.5/100000 in 2006 with a general decline in all age groups in both sexes except for the youngest age group (age 15-24), in which the rate has been relatively stable (Figure 2). The risk of suicide is highest in the older age groups, and especially in men with a relative risk 2-3 times higher than in women (NASP, 2008).

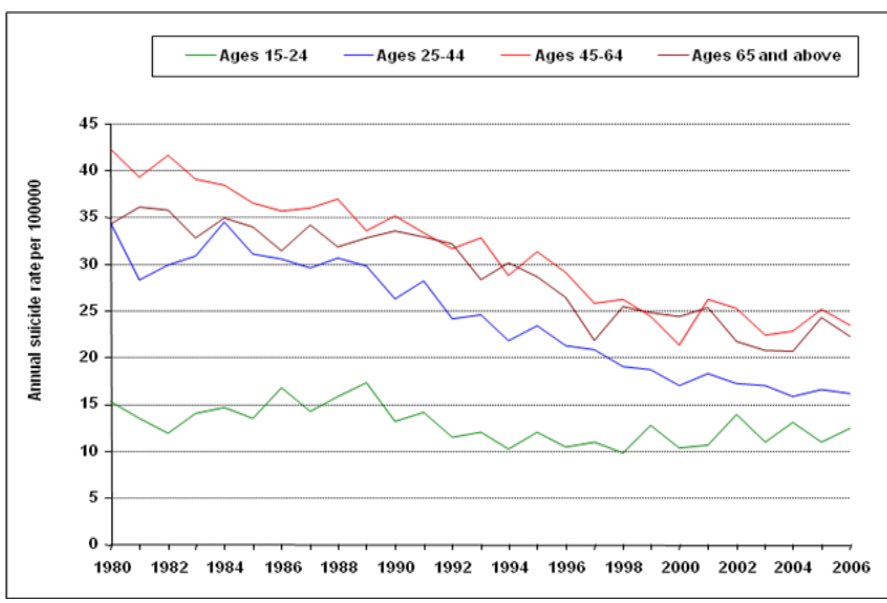

Figure 2. Suicide rates in Sweden 1980-2006 in different age groups (NASP, 2008).

It is estimated that attempted suicide is up to 20 times more frequent than completed suicide (WHO, 2008). In Sweden reported suicide attempts occur at an annual rate of 110/100000 (year 2004) with an increase in more recent years. Contrary to suicide attempted suicide is more common among females and in the younger age groups. In more recent years there has been a significant increase in the frequency of reported suicide attempts among younger women aged 15-24 (NASP, 2008). The real number of attempted suicide is probably much higher since the ones recorded are only those that come to the attention of the health services.

1.4 Suicide and Suicidal Behavior in Schizophrenia Spectrum Psychosis

It has been estimated from psychological autopsies that more than 90% of those dying by suicide have a diagnosable psychiatric disorder at the time of death and with approximately 60% of the suicides occurring in relation to mood disorders. Other psychiatric disorders at high risk for suicide include schizophrenia, substance abuse, alcoholism and personality disorders (Mann, 2003). The risk of suicidal behavior is not only dependent on the main psychiatric disorder. Although the presence of a psychiatric disorder is a main risk factor relatively few commit suicide, indicating the importance of a predisposition to suicidal behavior that is independent of the main psychiatric disorder. A stress-diathesis model has been suggested (Figure 3) in which the diathesis in addition to the psychiatric disorder is taken into account in determining the risk of suicidal behavior (Mann et al., 1999).

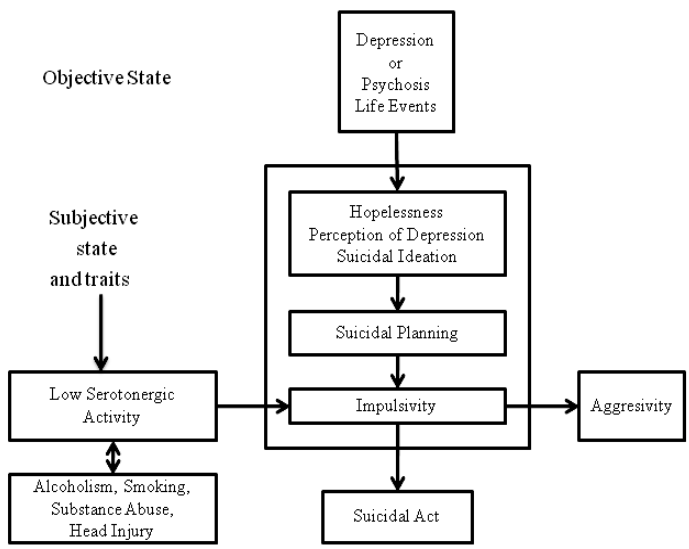

Figure 3. A model of suicidal behavior (Mann et al., 1999).

For example, a worsening of the psychiatric disorder can be a typical stressor but an acute psychosocial crisis often appears to be the most proximal stressor leading to suicidal behavior. Several factors influence the diathesis leading to this behavior; such traits as aggression, pessimism and impulsivity may be important factors (Mann et al., 1999; Turecki, 2005) in addition to gender, religion, familial/genetic factors and

childhood experiences. Environmental risk factors include alcoholism and substance abuse, head injury, and stress during pregnancy and childhood such as restricted fetal growth, toxic exposure and maltreatment and neglect in childhood (Mann et al., 1999; Mann, 2003). Neurobiological correlates such as low serotonin activity may also influence the stress-diathesis model of suicidal behavior and will be discussed later in detail.

Suicide is a major cause of death among patients with schizophrenia and psychotic disorders. Most studies on suicide and psychosis have only included schizophrenia and not the broader spectrum of psychotic disorders. The lifetime prevalence of suicide in patients with schizophrenia has been estimated to be ten times higher than among the average population (Baxter and Appleby, 1999). Earlier research has suggested suicide rates up to 13% among patients with schizophrenia (Caldwell and Gottesman, 1990) but more recent studies, taking into account the variable suicide risk during the life span, i.e. a higher risk close to illness onset and thereafter a declining risk, report a life time suicide mortality of 4-5% (Inskip et al., 1998; Palmer et al., 2005). The more recent study by Palmer combined two different approaches for a more exact specification of lifetime suicide risk. Proportionate mortality is calculated by dividing the number of subjects who have died from suicide by the number of subjects who have died from all causes during the time of follow-up. Most of the time this will overestimate the lifetime suicide risk since subjects are rarely followed during their entire lives. The second approach is case fatality which is the percentage of the total sample that died by suicide, this method risks missing future suicides and might thus provide a low estimate of lifetime prevalence. Another way of calculating suicide risk is the use of the standard mortality ratio (SMR). This is calculated by dividing the observed mortality of a cohort with the expected mortality of an age and gender-matched cohort representative of the general population.

The SMR is increased in patients with schizophrenia and the SMR for suicide was 15.7 for males and 19.7 for females in an epidemiological cohort of Swedish patients (Ösby et al., 2000). SMRs in suicide were especially high in young patients in the first year after the first diagnosis. Although the risk of suicide is considered to be highest in the early years of disease some studies suggest that the risk remains over a very long period of up to four decades after an index suicide attempt (Heilä et al., 1997; Suominen et al., 2004). Suicide risk in schizophrenia has been considered to be higher in male patients (De Hert et al., 2001; Limosin et al., 2007; Ran et al., 2007). Part of the explanation for the lower suicide risk in females could be that women have a later onset of disease, thereby decreasing the numbers of years at risk and usually use less lethal methods when attempting suicide (Häfner, 2003). However, a recent review concluded that most of the studies on suicide risk in schizophrenia examined did not take sex into account and suggestions have been made for future research to further examinine the role of sex (Lester, 2006) and a recent Swedish population-based case-control study concluded that gender did not significantly affect suicide risk (Reutfors et al., 2009) in schizophrenia.

Clinical assessment of suicide risk is a difficult and demanding task in everyday clinical work given the many factors involved in the suicidal process and the limited specificity of clinical predictors of suicide. Although the risk of suicide is considered to be high the real number of patients eventually dying by suicide is low. Few clinical suicide assessment tools for schizophrenic patients live up to reasonable expectations (Preston and Hansen, 2005).

Risk factors for suicide in schizophrenia spectrum psychosis appear to be less associated with typical core symptoms of psychosis such as delusions and hallucinations but more with depressive symptoms such as agitation, hopelessness and feelings of worthlessness (Hawton et al., 2005) as well as other such risk factors as short duration of illness (Limosin et al., 2007), suicide plans, prior attempted suicide, substance abuse, depressive disorder and poor adherence to treatment (Taiminen et al., 2001; Kreyenbuhl et al., 2002; Sinclair et al., 2004; Hawton et al., 2005; Kuo et al., 2005; Tidemalm et al., 2008). Moderate to severe psychotic symptoms and a family history of suicidal behavior have also been found to be important risk factors (McGirr et al., 2006). Severity of illness as indicated by the number of admissions has also been suggested to be a determinant of suicide (Yarden, 1974; Roy, 1982). Higher educational attainment, age ≥30 years at onset of symptoms and a history of suicide attempts were associated with an increased risk of suicide within five years after a first clinical schizophrenia inpatient diagnosis in a newly published Swedish study (Reutfors et al., 2009). There were also tendencies toward an increased risk of suicide being associated with having been married or cohabiting, and with a longer total duration of hospitalization. Attempted suicide is common in schizophrenia spectrum psychosis and is considered to be the strongest clinical predictor of future suicide (Harris and Barraclough, 1997). It is estimated that 20-40% of schizophrenic patients attempt suicide (Pompili et al., 2007) and the methods used are often violent and lethal (Harkavy-Friedman et al., 1999; Hunt et al., 2006).

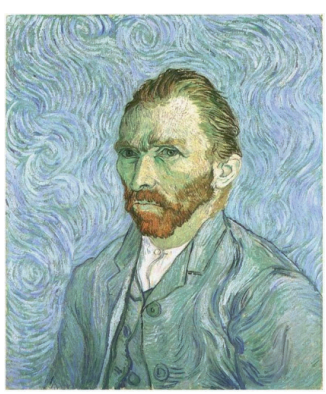

Figure 4. Self-portrait 1889. During the late years of life Vincent van Gogh (1850-1890) suffered from psychotic attacks and delusions. The artist attempted suicide by shooting himself in the chest. He survived, but died two days later from the wound.

1.5 Biomarkers of Suicide Risk in Schizophrenia Spectrum Psychosis

A complex system of the central nervous system (CNS) involving the monoamine neurotransmitter 5-hydroxytryptamin (5-HT or serotonin) is involved in mood, aggression and control of appetite. The system plays an important role in the regulation of such biological functions as sleep and general metabolism and is involved in different psychiatric disorders. The serotonin system plays a major role in depression and antidepressant medications such as tricyclic antidepressant (TCAs) and selective serotonin reuptake inhibitors (SSRIs) work through increasing the amount of serotonin in the synapses in the brain by inhibiting the reuptake of serotonin. The serotonin system has also been associated with other psychiatric conditions such as alcoholism, anxiety disorders and suicidal behavior.

Measurement of neurotransmitter metabolites in the cerebrospinal fluid (CSF) have been used to examine central monoamine turnover and are thought to reflect the events in the CNS (Åsberg, 1997) as suggested by indirect evidence (Stanley et al., 1985). The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in CSF is used as an indicator of central serotonin turnover and the turnover appears to be relatively stable over time and although repeated CSF studies are few in number and fraught with methodological problems, concentrations of CSF 5-HIAA have been considered to be a relatively enduring trait (Träskman-Bendz et al., 1984).

In 1976 Åsberg (Åsberg et al., 1976) found an association between low concentrations of CSF 5-HIAA and suicide in patients diagnosed with mood disorders. The patients with low 5-HIAA concentrations attempted suicide more often and more violently. This finding among depressed patients has been replicated several times (Åsberg, 1997) and findings of low serotonin concentrations in the postmortem brains of suicide victims have supported this initial finding (Stanley and Mann, 1983; Mann, 2003). The relationship between low concentrations of 5-HIAA and suicide risk appears to be well established in patients diagnosed with mood disorders (Nordström et al., 1994; Lester, 1995; Mann et al., 2006).

Few studies have, however, analyzed the relationship between suicidal behavior and CSF 5-HIAA in schizophrenia spectrum psychosis. Some studies support an association between dysfunction of the serotonin system and suicidal behavior in schizophrenia spectrum psychosis: for example, the antipsychotic drug clozapine affects the serotonin system and reduces suicidal behavior in schizophrenia (Meltzer et al., 2003). Suicide attempters in general are more impulsive than psychiatric controls (Harkavy-Friedman et al., 1999) and studies have found an association between low concentrations of CSF 5-HIAA, lifetime aggressivity and lethality of suicide attempt (Träskman-Bendz et al., 1992; Mann et al., 1996). The serotonin dysfunction has been linked to impulsive, aggressive traits and hopelessness, which may be a clinical mediator of suicidal behavior, as well as depression (Placidi et al., 2001; van Heeringen, 2001; Van Heeringen and Marusic, 2003), which is an important risk factor for suicide in schizophrenia (Hawton et al., 2005). However, the direct results from

studies dealing with an association between concentrations of CSF 5-HIAA and suicide in schizophrenia spectrum psychosis are contradictory, mainly because of small numbers of patients and short periods of follow-up.

Van Praag (van Praag, 1983) found lower concentrations of CSF 5-HIAA in suicide attempters on comparing ten non-depressed patients with schizophrenia with a recent suicide attempt with ten non suicidal schizophrenic patients and ten controls. Ninan (Ninan et al., 1984) reported lower concentrations of CSF 5-HIAA in schizophrenic patients on comparing eight suicide attempters with eight non-attempters. Banki (Banki et al., 1984) found lower concentrations of CSF 5-HIAA in schizophrenic suicide attempters than in non-attempters. Among attempters only those using violent methods had significantly lower CSF 5-HIAA concentrations than the non-attempters. In a long-term study in which 30 schizophrenic patients were followed for 11 years the suicide attempters had significantly lower concentrations of CSF 5-HIAA (Cooper et al., 1992). No difference in CSF 5-HIAA concentrations between attempters and non-attempters was reported in two studies among patients diagnosed with schizophrenia and schizoaffective disorder (Roy et al., 1985; Lemus et al., 1990). Pickar (Pickar et al., 1986) were unable to find an association between a past history of attempted suicide and concentrations of the CSF monoamine metabolites 5-HIAA and homovanillic acid (HVA) in 28 inpatients with schizophrenia (Table 1).

Table 1. CSF 5-HIAA concentrations and suicidal behavior in schizophrenia spectrum psychosis (nM/L).

Author	**Suicides**	**Attempted suicides**			**Psychiatric controls**			**Levels correlated with height/sex**	**Conclusion**
	n	**mean**	**SD**	**n**	**mean**	**SD**	**n**		
Banki et al., 1984	0	95	24	9	126	35	37	Yes/Yes	Lower in violent attempters
Cooper et al., 1992	0	35	36	10	123	131	20	No/No	Lower in attempters
Lemus et al., 1990	0	195	60	6	166	59	16	No//No	No difference
Ninan et al., 1984	2	NR	NR	8	NR	NR	8	No/Yes*	Lower in attempters
Pickar et al., 1986	0	83	6	2	95	38	26	No/No	No difference
Roy et al., 1985	0	108	17	27	112	9	27	No/No	No difference
Van Praag et al., 1983	0	NR	NR	10	NR	NR	10	No/No	Lower in attempters

SD, standard deviation. NR, not reported. *Compared men only in both groups.

Dopamine is a monoamine neurotransmitter of the nervous system and also the precursor of norepinephrine and epinephrine. Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement, motivation and reward, inhibition of prolactin production (involved in lactation), sleep, mood, attention, and learning. Abnormally high dopamine action has been strongly linked to psychosis and schizophrenia and for many years this idea was supported by indirect pharmacological evidence. Blockage of dopamine receptors was found to reverse the psychotic symptoms and modern antipsychotic medication block dopamine function to varying degrees.

Homovanillic acid (HVA) is the main dopamine metabolite in the CSF and used to measure central dopamine turnover (Stanley et al., 1985). Although the dopamine system is found to be abnormal in depression and attempted suicide in depression has been linked with low CSF HVA concentrations (Träskman et al., 1981) few post-mortem and retrospective studies have examined the role of dopamine and suicidal behavior and the results are considered to be inconclusive (Mann, 2003). Studies analyzing CSF HVA and suicidal behavior in schizophrenia spectrum psychosis are few in numbers with both negative results (Roy et al., 1985; Banki et al., 1986; Pickar et al., 1986; Cooper et al., 1992) and a tendency towards lower CSF HVA concentrations in suicide attempters (Banki et al., 1984) and demands for more studies have been made (Lester, 1995).

The ratio between the monoamines HVA and 5-HIAA in the CSF has been suggested to be a description between the turnover of dopamine and serotonin and a way to investigate an imbalance between these monoamines (Roy et al., 1986). The ratio can be used as an indicator of impaired serotonergic influence on dopamine activity (Ågren et al., 1986). Some studies have found an association between a low ratio of CSF HVA/CSF 5-HIAA and suicidal behavior (Roy et al., 1986; Engström et al., 1999) and suicidal intent in suicide attempters (Jokinen et al., 2007). In these studies most of the patients were diagnosed with mood disorders and very few had a diagnosis within the schizophrenia spectrum. For patients with schizophrenia spectrum psychosis the importance of the HVA/5-HIAA ratio remains unclear due to a lack of studies.

1.6 Schizophrenia Spectrum Psychosis and Mortality

People suffering from severe psychiatric disorders have an excess mortality from both natural and unnatural causes compared to people with no psychiatric disorder. Patients with schizophrenia spectrum psychosis have a higher mortality from natural causes than patients with other psychiatric disorders (Laursen et al., 2007), and the mortality is estimated to be two to three times higher than that observed in the general population, mainly associated with suicide but also with increased mortality from other causes (Brown, 1997; Ösby et al., 2000; Auquier et al., 2007). During the last few decades there has been a major shift in the treatment of schizophrenia spectrum psychosis with many patients who were previously subjected to inpatient care now being treated outside hospitals and the mortality among these patients is rising (Hansen et al., 2001;

Seeman, 2007) and also the mortality gap between the general population and schizophrenia patients has worsened in recent decades (Saha et al., 2007).

Epidemiological data show that more excess death is caused by natural deaths than by unnatural causes of death, with cardiovascular disease and cancer being the most common causes of death (Mortensen and Juel, 1993; Ösby et al., 2000). However, the specific causes of death giving rise to excess mortality were suicides in males and cardiovascular disease in females in a Swedish study (Ösby et al., 2000). Aside from suicide unnatural causes of death such as accidents are common (Allebeck et al., 1986; Brown, 1997; Ösby et al., 2000).

Although the natural causes of death are the same, the higher mortality may be related to causes that reflect a dimension of poor judgment, risk-taking and impulsivity (Faustman et al., 1993) and lifestyle factors such as smoking, lack of exercise, and an unhealthy diet may contribute (Brown et al., 1999) as well as other factors such as side effects from anti psychotic medication (Allison et al., 1999). Impulsivity, which may play an important role in the mortality of patients with schizophrenia spectrum psychosis, is linked with the serotonin system and has been correlated with low concentrations of CSF 5-HIAA in several psychiatric disorders (Brown and Linnoila, 1990; Lidberg et al., 2000; Stanley et al., 2000; Placidi et al., 2001). Faustman (Faustman et al., 1993) found a correlation between low CSF 5-HIAA concentrations and early mortality from other causes than suicide in a mixed psychiatric sample implicating CSF 5-HIAA in a broad behavioral dimension of impulsivity. During more recent years it has become increasingly clear that an integrated approach is needed to be able to intervene against the high mortality found in patients with schizophrenia spectrum psychosis.

1.7 The Kynurenic Acid Hypothesis of Schizophrenia

The glutamatergic system plays a crucial role in memory formation and information processing in the brain and the neurotransmitter glutamate is an abundant excitatory neurotransmitter in the central nervous system.

For several decades the leading hypothesis pertaining to the etiology and pathophysiology of schizophrenia has been hyperactivity of the dopaminergic system in the brain, mainly supported by indirect pharmacological evidence. However, during the last few years, evidence for dysfunction of the glutamatergic system in schizophrenia has also emerged (Carlsson et al., 2001; Schwarcz et al., 2001). The tryptophan metabolite kynurenic acid (KYNA) is a naturally occurring antagonist of the glutamate receptor N-methyl-D-aspartate (NMDA) in the brain (Parsons et al., 1997). Compounds such as phencyclidine (PCP) and ketamine that block NMDA receptors have been found to induce psychotic symptoms as well as cognitive deficits in healthy humans and aggravate psychotic symptoms in schizophrenic patients (Jentsch and Roth, 1999). KYNA, an endogenous tryptophan metabolite, antagonizes both the NMDA receptor (Kessler et al., 1989) and the cholinergic alpha7* nicotinic receptor (Hilmas et al.,

2001) in the brain. Elevated concentrations of this compound have previously been found in the CSF (Erhardt et al., 2001; Nilsson et al., 2005) and in the postmortem prefrontal cortex (Schwarcz et al., 2001) of patients with schizophrenia thus supporting the glutamate theory of schizophrenia. Positive correlations between CSF concentrations of KYNA, HVA and 5-HIAA have been found in male schizophrenic patients suggesting that elevated concentrations of CSF KYNA are associated with an increased turnover of dopamine and serotonin (Nilsson-Todd et al., 2007).

In a recent study on patients diagnosed with major depressive disorders with a recent suicide attempt elevated concentrations of KYNA were found (Linderholm et al., 2009). However, to the best of our knowledge, no study has examined the correlation between suicidal behavior and CSF KYNA concentrations in patients with schizophrenia spectrum psychosis.

2 AIMS

The general aims of this thesis were to investigate the impact of gender, monoamine metabolites and attempted suicide on the long-term suicide risk in patients with schizophrenia spectrum psychosis, to assess the impact of monoamine metabolites on mortality from natural causes and to investigate an association between CSF KYNA, severity of disease and suicidal behavior. The more specific aims were formulated as follows.

-Investigate the long-term suicide risk and cumulative suicide risk by means of survival analysis in relation to gender.

-Investigate the impact of attempted suicide on long-term suicide risk by cumulative survival, predictive values, and odd ratios.

-Investigate the relationship between concentrations of the CSF monoamine metabolites 5-HIAA, HVA and the HVA/5-HIAA ratio, attempted suicide and suicide.

-Investigate the relationships between CSF KYNA concentrations at the onset of illness and suicidal behavior and whether concentrations of CSF KYNA at the onset of illness are associated with the severity of disease as measured by the proportion of days admitted to a psychiatric inpatient department during the follow-up period.

-Investigate whether low concentrations of CSF 5-HIAA and HVA might predict early death from other causes than suicide.

3 MATERIAL AND METHODS

3.1 Patients

In studies I and III the cohort consisted of 385 inpatients (153 men, 232 women) admitted to a psychiatric university clinic in Stockholm during the years 1973-1987 with symptoms of a schizophrenia-like nature. After admittance the patients were asked to participate in biological and/or pharmacological research. The cohort consists of all patients who gave their consent to participate (Bjerkenstedt et al., 1977; Wode-Helgodt et al., 1977; Härnryd et al., 1984; Oxenstierna et al., 1996).

Study II consisted of a subgroup from study I compromising a total of 224 inpatients (77 men, 147 women). For this subgroup information about attempted suicide had been retrieved from the medical records.

The patients in study IV consisted mainly of a subgroup from study III. Some of the patients have been described earlier by Nilsson (Nilsson et al., 2005). The sample consisted of 59 patients (35 men, 24 women) who were admitted and hospitalized between the years 1979-1987.

Study V consisted of the patients described in studies I and III who died during the follow-up period. In total 97 patients died during the follow-up period, 26 from suicide and were excluded in this study, 71 (21 men, 50 women) from other causes: natural, undetermined and accidental causes.

The follow-up period for every participant started at the index admission when a lumbar puncture was performed and was until the end of July 2006 or at time of death.

3.2 Lumbar Puncture

The lumbar puncture employed in studies III and IV was performed in a standardized manner between 8 a.m. and 9 a.m. after the subject had been at bed rest for at least eight hours. Drug treatment was withheld until puncture had been performed in patients in study III. Twelve milliliters of CSF were drawn (Sedvall and Wode-Helgodt, 1980). The CSF was immediately centrifuged and stored at below -20°C. CSF 5-HIAA and HVA concentrations were determined by mass fragmentography (Swahn et al., 1976). CSF KYNA used in study IV was analyzed by means of an isocratic reversed-phase high-performance liquid chromatography system connected to a fluorescence detector (Nilsson et al., 2005).

3.3 Diagnostic Methods

All patients in studies I-V were searched for in the registry of the Central Bureau of Statistics to identify those who had died. The reported causes of death were obtained from the Causes of Death Register at the National Board of Health and Welfare. This

register contains information on all deaths from 1961 and onwards and is more than 99% complete (Statistics Sweden, 2009).

All discharge ICD diagnoses made during inpatient care periods and submitted to the Swedish Inpatient Register were used and assessed in retrospect to obtain a lifetime main diagnosis using a hierarchy as described earlier (Ekholm et al., 2005; Vares et al., 2006). This diagnostic procedure has been shown to agree in about 94% of cases with traditional research diagnoses of schizophrenic psychosis according to the Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) and the fourth edition (DSM-IV) (Ekholm et al., 2005; Vares et al., 2006).

Patient main lifetime diagnoses included schizophrenia spectrum psychosis diagnoses: schizophrenia, delusional disorder, psychosis not otherwise specified, schizophreniform disorder and schizoaffective disorder. A small number of the patients received a lifetime main diagnosis outside the non-organic psychotic spectrum.

The Swedish Inpatient Register was started in 1971 and it has been mandatory since 1973 for all psychiatric hospitals to report all admissions, discharges and diagnoses to the Register. The patient´s discharge diagnosis is recalled and recorded by the psychiatrist in charge. All death certificates were read and evaluated, and deaths of undetermined causes or accidents have been classified according to the information obtained. We concluded, based on the information from the death certificates, that there were no hidden suicides.

3.4 Statistical Methods

Suicide rates were calculated using the person-time method (number of suicides divided by person-years of follow-up). Sensitivity (i.e. the probability that a person who dies by suicide has previously attempted suicide), specificity (i.e. the probability that a person who did not die by suicide had not attempted suicide), the positive predictive value (i.e. the probability that a person who attempted suicide died by suicide), and negative predictive value (i.e. the probability that a person who did not attempt suicide did not die by suicide) and odds ratios (OR) were used in study II.

Statistical analyses were performed using the JMP statistical package version 7 (SAS Inc., 2007) in all studies. Student´s t-tests and the Kruskal-Wallis test were used to analyze the continuous variables. Fisher´s exact test for dichotomous variables was used to evaluate the between-group comparisons. Logistic regression models were used to adjust for confounding factors. The significance level was set at $p<0.05$.

3.5 Ethical Aspects

The Regional Ethical Review Board in Stockholm approved the study protocol for this thesis on the 10th of May 2006 (2006/408-31/4).

4 RESULTS AND CONCLUSIONS

4.1 Study I: Long-Term Suicide Risk in Schizophrenia Spectrum Psychoses: Survival Analysis by Gender

Results

During the period of follow-up 26 (6.8%) patients died by suicide, 10 (6.5%) men and 16 (6.9%) women. The cumulative suicide risk was 8.2% for men and 9.5% for women (not significant (NS)) (Figure 5). There was no significant difference between genders in suicide risk or cumulative suicide risk. The mean period of follow-up was 23.5 (SD ± 6.8) years for men and 25.9 (SD ± 8.1) years for women (NS). The mean period from the index admission to the time of suicide was 7.7 years (SD ± 5.2) for men and 7.8 years (SD ± 8.6) for women (NS). Women were older at time of lumbar puncture (33.8 ± 10.3 years vs. 29.8 ± 7.9 years, $p < 0.0001$) and age was only found to be a predictor of suicide in women. The suicide rate was 278.4 per 100000 person-years for men and 276.3 per 100000 person-years for women (NS). Twelve suicides were violent and 14 were non-violent. Most committed suicide by self-poisoning (n = 10). Jumping from high places (n = 6) was the most common violent method.

Conclusions

The results from this study suggest that the suicide risk is high over a long period of time for both genders in schizophrenia spectrum psychosis.

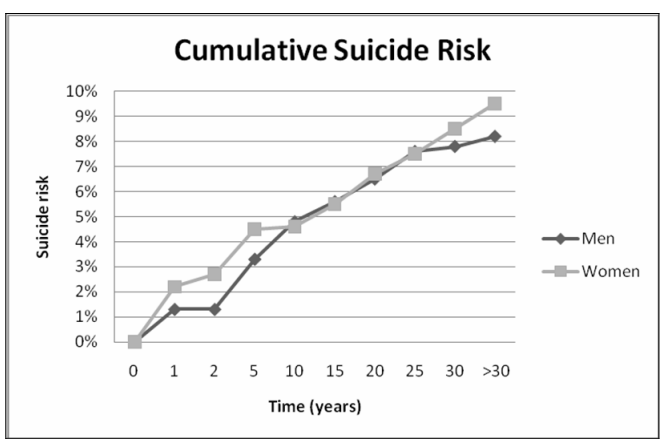

Figure 5. Cumulative suicide risk by gender in patients with schizophrenia spectrum psychosis.

4.2 Study II: Attempted Suicide Predicts Suicide Risk in Schizophrenia Spectrum Psychosis

Results

Two hundred and twenty four patients (77 men, 147 women) with recorded information about attempted suicide were followed for a mean time of 24.6 (SD ± 8.2) years with a longer follow-up period for women (women 25.4 (SD ± 8.8) years vs. men 23.0 (SD ± 7.8) years, $p = 0.04$). Eighty-two patients (37%) had a history of attempted suicide with similar proportions among men (32%) and women (39%) (NS). Eighteen (8%) died by suicide during the follow-up period, 9 (11.7%) men and 9 (6.1%) women (NS). Eleven of the suicides were violent. Seven of the men (78%) and eight of the women (89%) who died from suicide had a history of attempted suicide. There was a strong association between a prior suicide attempt and suicide ($p < 0.0001$). Suicide rates among suicide attempters were almost three times higher in male patients (men, 1589 per 100.000 person years vs. women, 589 per 100.000 person years, $p < 0.0001$). Odds ratios and predictive values are presented in Table 2. Survival analyses with cumulative survival curves are presented for the total cohort (Figure 6) and for suicide attempters (Figure 7).

Conclusion

Attempted suicide is an important risk factor for suicide in both men and women with schizophrenia spectrum psychosis, particularly in male suicide attempters.

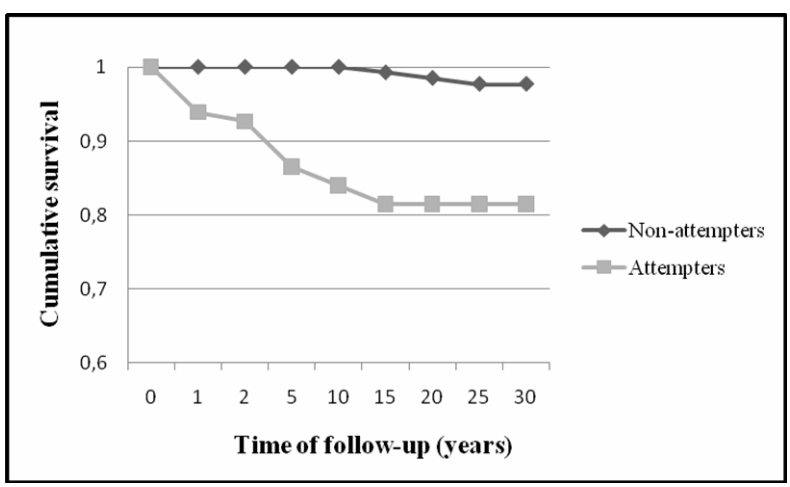

Figure 6. Cumulative survival curves for total cohort, non-attempters vs. attempters (n=224).

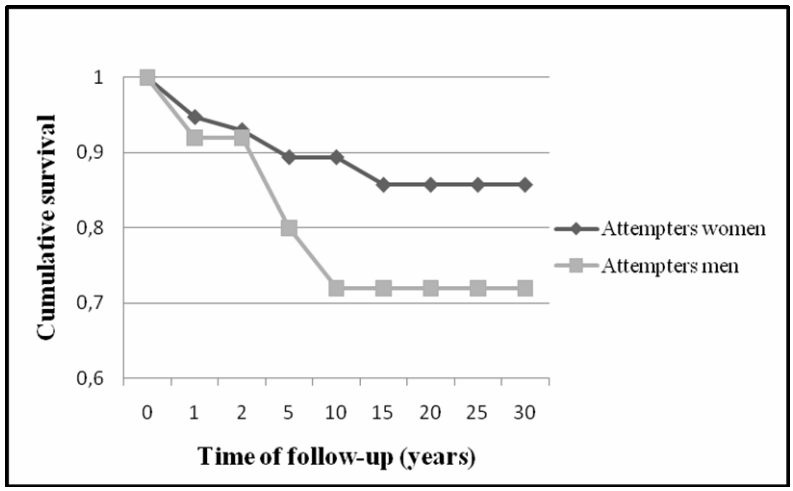

Figure 7. Gender specific cumulative survival curves for suicide attempters by gender.

	Men		Women	
Suicide	Yes	No	Yes	No
Attempters, counts	7	18	8	49
Non-attempters, counts	2	50	1	89
Positive predictive value, %	28		14	
Negative predictive value, %	96		99	
Specificity, %	74		64	
Sensitivity, %	78		89	
Odds ratio	9.72		14.53	
Odds ratio 95% CI	1.85-51.20		1.77-119.60	

Table 2**.** Gender-specific specificity, sensitivity, predictive values, and odds ratios of attempted suicide for suicide.

4.3 Study III: CSF 5-HIAA, Attempted Suicide and Suicide Risk in Schizophrenia Spectrum Psychosis

Results

The patients in the cohort, described earlier in Study 1 (n = 385: 153 males, 232 females) were all lumbar punctured at the index admission. CSF 5-HIAA, CSF HVA, and their ratio were investigated in relationship to suicide and attempted suicide. Most of the patients received a lifetime main diagnosis of schizophrenia (59.5%), psychosis not otherwise specified (9.6%) and schizoaffective disorder (7.5%). Of these patients 5.2% received a lifetime main diagnosis of delusional disorder, 4.9% of schizophreniform disorder and 4.9% of mood disorder. The remaining patients´ diagnoses were outside the non-organic schizophrenia-related or psychotic mood disorders. No difference was found between CSF 5-HIAA concentrations in patients who died and those who did not die by suicide (106.2 ± 33.6 vs. 104.4 ± 40.5 nanomol [nM], NS). No gender difference was found when the sexes were compared separately. Neither were there any differences between suicide attempters (n = 82) and non-attempters (n = 142). CSF HVA concentrations did not differ between patients who died and did not die by suicide (200.5 ± 90.1 nM vs. 192.0 ± 94.6). Neither did CSF HVA levels differ between suicide attempters and non-attempters. On investigating the HVA/5-HIAA ratio no difference was found when comparing suicide and non-suicide patients or suicide attempters and non-attempters. The results were the same on adjusting for the height of the patients. Male gender (OR = 3.5) and attempted suicide (OR = 12.4) were strong predictors of future suicide in a multiple regression model taking age, height, and monoamine metabolites into account.

Conclusion

Suicidal behavior in patients with schizophrenia spectrum psychosis may not, in contrast to patients with mood disorder, be predicted by concentrations of the monoamine metabolites 5-HIAA, HVA or their ratio in CSF. This study confirms earlier findings that male gender and attempted suicide are important risk factors for suicide and suggests a lesser importance of serotonin dysfunction in suicidal behavior in schizophrenia spectrum psychosis.

4.4 Study IV: Early Death and CSF Monoamine Metabolites in Schizophrenia Spectrum Psychosis

Results

During follow-up 97 (27%) of the 385 patients died in the cohort earlier described (studies I and III), 26 (7%) by suicide, 6 (2%) in accidents, 3 (0.8%) of undetermined causes, and 62 (16%) of natural causes. The median age at death was 54.6 years for all deceased patients. Results with regard to death by suicide were excluded and the remaining deceased patients were divided by the median age into two groups (Tables 3

and 4). The median age at death for non-suicidal deceased patients was 59.2 years (mean 60.1 years, n=71, 21 men and 50 women). The majority of these patients died of natural causes (Table 3) and had a lifetime main diagnosis of schizophrenia (Table 4). There was no significant difference in follow-up times between the younger and older deceased persons. CSF 5-HIAA and HVA concentrations for the younger deceased individuals (109 ± 38 and 177 ± 82 nM) were significantly lower than for the older deceased persons (116 ± 37 and 240 ± 111 nM, p = 0.04 and p = 0.008, respectively). In a regression model taking into account such confounders as height and age at lumbar puncture no significant correlations between CSF 5-HIAA and HVA concentrations and age at death below the median split were found. Thus, our finding could be explained by these confounders, which are known to influence the concentrations of monoamine metabolites in the CSF. No significant difference in CSF 5-HIAA and HVA concentrations was found between accidental (n = 6), undetermined (n = 3) and natural (n = 27) deaths of the younger deceased patients. Information about suicide attempts were obtained for 55 of the deceased patients (suicide attempters n = 18, non-attempters n = 37). There was no significant difference in the follow-up period between attempters and non-attempters.

Conclusion

We did not find any association between early death from natural and unnatural causes of death excluding suicides and CSF monoamine metabolite concentrations. Unnatural causes of death such as accidents are common in patients with schizophrenia spectrum psychosis.

Cause of death	**Deceased below median split ≤ age 59.2**	**Deceased above median split >age 59.2**
	n	**n**
Cardiovascular	6	18
Cancer	11	6
Infection	4	4
Gastrointestinal	3	5
Respiratory	2	2
Neurological	1	0
Accident	6	0
Undetermined	3	0

Table 3. Causes of death for patients below and above median split.

Diagnosis	Deceased below median split ≤ age 59.2	Deceased above median split >age 59.2
	n	n
Schizophrenia	29	20
Schizophreniform disorder	0	3
Schizoaffecive disorder	0	4
Psychosis not otherwise specified	3	3
Personality disorder	1	0
Bipolar disorder	1	0
Delusional disorder	0	3
Other	2	2

Table 4. Lifetime main diagnoses for patients above and below the median split.

4.5 Study V: CSF Kynurenic Acid and Suicide Risk in Schizophrenia Spectrum Psychosis

Results

Fifty-nine patients (35 males, 24 females) hospitalized at the onset of illness with schizophrenia-like symptoms were followed for a mean period of 22.1 ± 5.5 years with no difference between the sexes. All patients were lumbar punctured and CSF KYNA concentrations were recorded at the index admission. Three died (5%) by suicide during the follow-up period (1 man, 2 women). The mean number of days admitted to a psychiatric inpatient department was 44.2 ± 64.3 days per year with no gender difference. It was possible to retrieve medical records for 39 of the patients. On analyzing these records, there was no evidence of attempted suicide for 30 (77%) of the patients, whereas 9 (23%) had a history of attempted suicide. No association was found between concentration of CSF KYNA and suicidal behavior (suicide and attempted suicide) and the number of days admitted to a psychiatric inpatient department.

Conclusion

In this long-term study of patients with schizophrenia spectrum psychosis, no association was found between concentrations of CSF KYNA at the onset of illness and suicidal behavior or the number of days of admission to a psychiatric inpatient department. The kynurenic acid hypothesis of schizophrenia is relatively new and hardly any studies have examined the correlation between CSF KYNA concentrations and clinical parameters. More studies are needed.

5 GENERAL DISCUSSION

The suicidal drive of patients with schizophrenia had already been described by Eugen Bleuler in 1911 as "the most serious of schizophrenic symptoms" and a number of studies since then have confirmed the high risk of suicide in patients with schizophrenia spectrum psychosis. Earlier studies have estimated lifetime suicide rates of up to 13% (Caldwell and Gottesman, 1990) but this number may have been overestimated. In study I we found that 6.8% of our patients died by suicide during the period of follow-up and this result is quite in line with Palmer´s recent meta-analysis (Palmer et al., 2005) where the lifetime suicide risk was estimated to be approx. 5% on combining proportionate mortality and case fatality for a more accurate estimation of the lifetime suicide risk. We were not able to find a gender difference in either the suicide rate or the cumulative suicide risk which is in contrast findings in the general population (WHO, 2008), and to most other studies examining gender differences in suicide risk among patients with schizophrenia and related disorders where male gender has been a risk factor for suicide (Caldwell and Gottesman, 1990; Brown, 1997; De Hert et al., 2001; Lester, 2006; Limosin et al., 2007) although gender did not affect the suicide risk in a recent Swedish study (Reutfors et al., 2009). A recent review by Lester (Lester, 2006) investigating gender differences in suicide risk concluded that it is a serious omission that the majority of studies on suicide in schizophrenia did not distinguish the results by gender. The inclusion of inpatients only suggests that our cohort consisted of patients with more severe disease, which is a risk factor for suicide (Kelly et al., 2004). Most of these studies have been on patients diagnosed only with schizophrenia not including the broader spectrum of psychosis included in our study. The lifetime main diagnosis of our patients was given in retrospect based on the diagnoses in the Swedish Inpatient Register. It has been concluded that the diagnoses based only on Swedish patients records show good to excellent agreement with diagnoses based on records and interviews and are adequate for assessing of lifetime diagnoses (Ekholm et al., 2005). The use of clinical register data over long periods of time may be susceptible to such time trends as changes in diagnosis classification (Munk-Jörgensen and Mortensen, 1992; Kendell et al., 1993) but the use of a wider diagnostic spectrum (such as schizophrenia spectrum psychosis) may reduce this effect (Ösby et al., 2000).

The risk of suicide is considered to be highest in the early course of illness in schizophrenia, especially within the first years of illness (Radomsky et al., 1999; Kuo et al., 2005), however, studies with a first-episode cohort and covering a period close to the onset of illness usually have higher estimates of the excess mortality from suicide than studies with longer periods of follow-up (Brown, 1997). We had a very long period of follow-up in our study with a median of 26 years. The high risk of suicide in our patients accumulated over a long time after the index admission and onset of illness (Figure 8), which stresses the importance of a clinical evaluation of the suicide risk by the treating physician not only in patients in the early years of disease, but also in

patients with chronic or relapsing disease, especially among those with a prior history of attempted suicide.

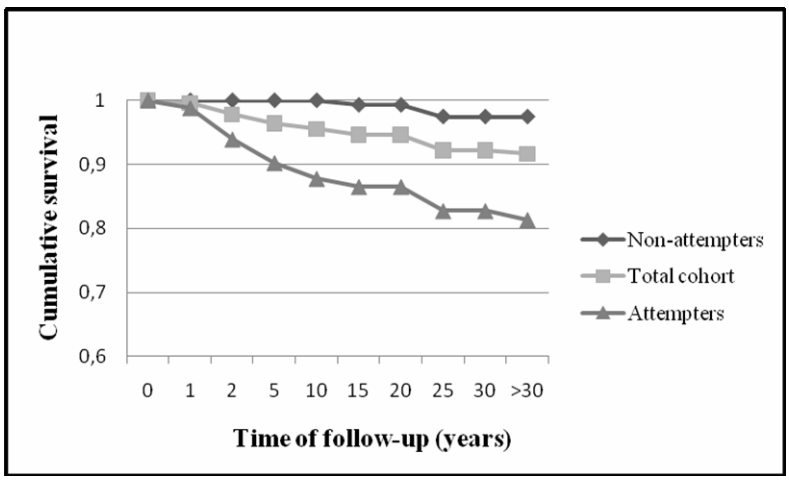

Figure 8. Cumulative survial after onset of illness in total cohort, non-attempters and suicide attempters.

Attempted suicide is common in patients with schizophrenia spectrum psychosis with estimates ranging from 20 to 40% (Pompili et al., 2007) and the methods used are often violent and lethal (Harkavy-Friedman et al., 1999; Hunt et al., 2006). The risk of attempted suicide in our cohort in study II was 37% with no difference between the genders. Attempted suicide is considered to be a strong risk factor for suicide (De Hert et al., 2001; Hawton et al., 2005) and this was confirmed in our study, especially among the male patients where suicide attempters had a 28% risk of eventually dying by suicide compared to 14% in female suicide attempters and a relatively low risk (1-4%) for patients without a history of attempted suicide to eventually die by suicide. The suicide rate was almost tripled in the male attempters compared to the female. Attempted suicide is more common in females in general but this was not the case in our study which has an enriched sample of patients using hospitalization as a selection criterion. Our result is in line with a recent meta-analysis of deliberate self-harm including both attempted suicide and acts in which other motives may have been more prominent where no gender difference was found in patients with schizophrenia and related diagnoses. Significant factors for deliberate self harm were past or recent suicide ideation, previous episodes of deliberate self-harm, past depressive episodes and a higher mean number of psychiatric admissions (Haw et al., 2005). It is important to note that using medical records to retrieve information about attempted suicide entails the possibility of underreporting since it is only the attempts that come to the knowledge of health professionals that are reported.

In contrast to earlier findings mainly among patients with mood disorders, where low concentrations of CSF 5-HIAA have been associated with attempted suicide and risk of

suicide (Nordström et al., 1994; Åsberg, 1997; Mann et al., 2006) we were not able to find an association between concentrations of CSF 5-HIAA and suicidal behavior in our cohort. Earlier studies analyzing suicidal behavior and monoamine metabolites in patients with schizophrenia spectrum psychosis are few in numbers and the results are contradictory (Table 1). A meta-analysis investigating an association between CSF HVA concentrations and suicidal behavior (Lester, 1995) yielded no support for an association, and this was also supported by our results. The CSF HVA/5-HIAA ratio has been suggested to be a measurement of imbalance between the turnovers of the monoamines (Roy et al., 1986). Earlier studies have found an association between suicidal behavior, suicidal intent and a low CSF HVA/5-HIAA ratio (Roy et al., 1986; Engström et al., 1999; Jokinen et al., 2007) but this was not supported by our findings. Most of these patients were diagnosed with mood disorders and only a few had a diagnosis within the psychotic spectrum. Indirect evidence for an association between serotonin dysfunction and suicidal behavior such as the importance of depression as a risk factor in schizophrenia (Drake and Ehrlich, 1985; Hawton et al., 2005), the reduction of suicidal behavior and suicide with the serotonin altering medication clozapine (Meltzer et al., 2003; Tiihonen et al., 2009) and the importance of aggressive and impulsive traits and hoplessness in suicidal behavior which are linked to the serotonin system (Placidi et al., 2001; Van Heeringen and Marusic, 2003) as well as the results from several reviews (Lester, 1995; Mann et al., 2006) support the involvement of the serotonin system and suicidal behavior in general, but there is a lack of direct evidence for an association between suicidal behavior, concentrations of CSF 5-HIAA and also HVA in schizophrenia spectrum psychosis.

The impact of the diagnosis on the relationship between CSF monoamine metabolites and suicidal behavior has not yet been completely investigated since most of the research has focused on patients with mood disorders. The evidence for an association between serotonin dysfunction and suicidal behavior may be related to certain diagnostic subgroups (mainly within the affective spectrum) and not to psychiatric disorders in general suggesting that the biological mechanisms underlying suicidal behavior in mood and psychotic disorders might be different. General concerns have been raised about various factors having an impact on the CSF monoamine neurotransmitter concentrations in biological suicide studies such as height and gender not being taken into account. Also the question of whether CSF monoamine metabolite concentrations reflect brain events can be raised. However, indirect evidence has shown that CSF markers are valid markers of brain events (Bulat and Zivkovic, 1971) and that the concentrations in the cerebral cortex and CSF are correlated (Stanley et al., 1985).
The concentrations of monoamine metabolites in CSF are also considered to be an enduring trait (Träskman-Bendz et al., 1984). The use of common constructs such as suicidality and aggression and their use in biological suicide research has also been questioned due to the inability to find an unambiguous relationship between CSF 5-HIAA concentrations and suicidality neither in general nor in subgroups of suicidal behavior (Roggenbach et al., 2002).

Patients with schizophrenia spectrum psychosis do not only die prematurely by suicide, they also have an increased mortality from other unnatural and natural causes, as demonstrated by several studies (Brown, 1997; Ösby et al., 2000) and the mortality gap between the general population and patients with schizophrenia has increased over the last few decades (Saha et al., 2007) with demands for immediate action being made. Although Faustman (Faustman et al., 1993) were able to find an association between early mortality and low concentrations of CSF 5-HIAA and HVA in his sample of patients with various psychiatric diagnoses perhaps reflecting an increased impulsiveness our findings did not support this association. We were not able to find an association between low concentrations of CSF 5-HIAA and HVA and early death but a large number of the patients in our cohort died in accidents. Patients with schizophrenia spectrum psychosis that die of natural causes die of the same causes that the general population does, but at an earlier age. An unhealthy lifestyle might contribute (Brown et al., 1999) as well as side effect from medication (Allison et al., 1999). Interestingly a recent study from Finland concluded that long-term treatment with antipsychotic medication is associated with lower mortality in patients with schizophrenia compared with no antipsychotic use. The drug clozapine appeared to be associated with a substantially lower mortality in general as well as a substantially lower risk of suicide than was any other antipsychotic medication (Tiihonen et al., 2009). The SMRs of newly diagnosed patients have been found to increase in Sweden both from natural and unnatural deaths (Ösby et al., 2000). The changes in the health system during recent decades, with a significant reduction in inpatient capacity might be an important factor explaining the rising mortality (Hansen et al., 2001; Seeman, 2007). An integrating approach covering both the medical and psychiatric needs of these patients is important and further interventions are needed to stop this trend.

Dopamine hyperactivity has been included in leading hypotheses explaining the etiology and pathophysiology of schizophrenia for several decades, but in recent years alternative hypotheses including evidence for glutaminergic dysfunctions have also received considerable attention (Carlsson et al., 2001; Schwarcz et al., 2001). On investigating an association between concentration of CSF KYNA at the onset of illness and suicidal behavior, as well as the severity of disease measured as proportions of days admitted to an inpatient department, we were not able to find an association. A recent study (Linderholm et al., 2009) found an increase in the CSF KYNA concentrations of individuals who recently performed a suicide attempt. However, these patients had a diagnosis of major depressive disorder. More studies are needed to investigate CSF KYNA and other neurochemical correlates with the outcome of schizophrenia spectrum psychosis. The recent findings suggesting glutamatergic dysfunction in schizophrenia may have potential consequences for the treatment and may influence the development of new medications.

6 FUTURE DIRECTIONS

In spite of advances in the treatment of psychiatric diseases in recent decades and a general decline in suicides in the western world suicide is still a major health problem with approximately one million suicides per year and an enormous social and economic burden worldwide. The mortality gap between the general population and patients with schizophrenia spectrum psychosis turn the focus not only on the treatment of the psychiatric disorders itself but also on somatic diseases and general health interventions. It has become increasingly clear that an integrated approach is needed to attack the problem. Intervention programs focusing on well-known life style risk factors, as well as appropriate use of antipsychotic medication might help reduce the mortality. The development of psychological interventions, inclusion of biological suicide research, involving neurochemical and genetic phenotypes, development of effective medical treatment, and improvement of clinical risk markers of suicide are all important areas of research. The use of functional brain imaging techniques makes it possible to investigate biochemical alterations and brain circuitry in relation to suicidal behavior. The discovery of neurochemical correlates underlying suicidal behavior in schizophrenia spectrum psychosis opens up new possibilities for pharmacologically acting agents.

Although patients with schizophrenia spectrum psychosis have a high mortality from both natural causes of death as well as suicides the absolute number of suicides is low. Still, the everyday risk evaluation remains a difficult and demanding task for the clinician.

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