Schizophrenia and Anxiety Disorders

MAGNITUDE OF THE PROBLEM

Comorbid anxiety disorders or symptoms are common in schizophrenia although differences in reporting are observed across cultures (Dixon et al.). Panic attacks in schizophrenia occurred in 45% of schizophrenia patients in the ECA. These individuals also had a high comorbidity with other psychiatric conditions and a higher cost of care.(Goodwin et al.). Similar figures were found in the community (Labbate et al. 99) with 43% of panic attacks (57% in paranoid patients). Past or current PTSD was found in 33% of patients. Actually PTSD was present in 14.3% of first admission psychosis in a clinical cohort of 426 patients (Neria et al.)

In a cohort of 100 consecutively presenting psychotic patients, Cosoff & Hafner found a prevalence of 45% for anxiety disorders, 13% for OCD, 17% for socialphobia in schizophrenia. No specific treatment of the anxiety disorder was provided in almost all cases.

The existence of a comorbid anxiety disorder correlates with positive and negative symptoms but not depression (Huppert et al.). The correlation with positive symptoms is the strongest, suggesting that the majority of anxiety is related to the acute exacerbation of schizophrenia (Emsley et al.).

Most of the time anxiety is considered secondary to the psychotic condition and is expected to improve in parallel with the Schizophrenic symptoms. [Benzodiazepines or sedative neuroleptics (Levomepromazine, Cyamemazine) with potent antihistaminic properties are often associated with the core antipsychotic treatment in schizophrenia presenting with an acute or sub-acute exacerbation for some weeks, as long as anxiety is present](see below).

Although anxiety impacts on the quality of life (Huppert et al.) and on the outcome (Emsley et al.) the existence of comorbid anxiety disorders is rarely explored. Such an evaluation should be systematic. Antipsychotic treatment may induce obsessive compulsive symptoms (OCS) (see below) and possibly social phobia symptoms (Pallanti et al.) that can be treated successfully with SSRI's. The treatment of agitation and OCD are presented separately.

A. ASSOCIATED SEDATIVE ANXIOLYTIC TREATMENT IN ACUTE PSYCHOTIC MANIFESTATIONS OF SCHIZOPHRENIA

The treatment of choice for acute schizophrenia is one of the newer generation antipsychotic drugs which are well-tolerated in the medium-term and can thus be used as maintenance therapy. In particular, drugs with little sedative effect are desirable in order to optimize functioning and preserve quality of life. Sedation is also undesirable as it may compromise management of negative symptoms. However, in certain patients who present with significant agitation and anxiety, drugs with low sedative

potential may not sufficiently attenuate these symptoms even though hallucinations, delusions and other positive treatments are satisfactorily managed. This 'residual' anxiety may interfere with compliance to medication, as well as being distressing to the patient. Two strategies are available to manage anxiety in such patients, namely the use of sedative antipsychotic drugs or the use of adjuvant benzodiazepine therapy.

Sedative antipsychotics, such as thioridazine, pipamperone, melperone, cyamemazine, a-flupenthixol, or levomepromazine can be used as treatment to manage both overt psychotic symptoms and anxiety (Garay et al., Meltzer et al., Squelart et al.). Once the patient is well-controlled, the treatment can be stopped or switched to a non-sedative antipsychotic for maintenance therapy. Several of these sedative antipsychotics have been shown to exert anxiolytic effects at low doses in non-psychotic patients and to relieve anxiety satisfactorily in schizophrenic patients at standard antipsychotic doses (Poldinger et al.).

Successful attenuation of anxiety and psychotic symptoms may also help in preventing the development of a full exacerbation (Carpenter et al.). Short-term adjuvant treatment with benzodiazepines can also be useful in managing patients presenting with marked anxiety and agitation (Barbee et al., Lingjaerde et al., Wolkowitz et al.). The benzodiazepine should be given in combination with non-sedative disinhibitory antipsychotics, such as several of the atypicals. The benzodiazepine should have potent anxiolytic action, low propensity for pharmacokinetic drug interactions and a long half-life to provide uninterrupted coverage. Benzodiazepine use should be restricted to as short a time as possible in order to prevent the risk of benzodiazepine dependence and rebound anxiety on treatment cessation. By the use of one of these two strategies, severe anxiety associated with acute psychotic episodes can be satisfactorily managed.

B. TREATMENT OF SCHIZOPHRENIA WITH OCD

For the treatment of schizophrenia with OCD the evidence is based on case reports and open studies.

Magnitude of the problem

In clinical samples the prevalence in schizophrenics of OCD was 14% in first episodes. (Poyurovsky et al.) 15.8% (Kruger et al.), 23.5% in chronic schizophrenics (Poyurovsky et al.), 15% for OCD & 29% for obsessive symptoms (OCS) (De Haan et al.). Patients with comorbid OCD are more disabled (Poyurovsky et al.)

Treatment

Antipsychotics are not effective in treating OCS in schizophrenia (Poyurovsky et al.).This was confirmed in an open prospective study in 113 patients (De Haan et al.) comparing risperidone & olanzapine. Typically, the initial score of the YBOCS =17.5 changes to 17.8 after 6 weeks treatment.

Conventional antiobsessive drugs (chlomipramine or SSRIs) are effective when used as augmentation treatment (Rahman et al., Poyurovsky et al., Dwivedi et al.). This is a statement commonly accepted although not based on convincing double blind trials.

Effect of antipsychotics on OCS
In schizophrenics, clozapine (Eales et al.,de Haan et al. ,Mc Cabe et al.) and olanzapine (Morrisson et al., Mottard et al., Lykouras et al.) are well known to exacerbate or to induce OCS. Case reports also exist with risperidone (Alevizos et al.) and quetiapine (Khullar et al.). Emergence of OCS was also described after clozapine withdrawal (Poyurovsky et al.).

Case reports of improvement of OCS in refractory OCD patients have also been reported with olanzapine (Potenza et al., Marazziti et al., Koran et al.), Risperidone (Jacobsen et al. ,McDougle et al.) including a double blind placebo controlled trial (McDougle et al.), Quetiapine (Denys et al., Mohr et al.).

C. Social phobia

Importance of the problem
As mentioned above, social phobia is frequent in schizophrenic patients (Cosoff & Hafner 1998, 17 %, Cassano et al. 1998, 17.7 %) in both studies social phobia was associated with psychotic features. In both studies almost none had a specific treatment for the associated anxiety disorder.

The nature and severity of social anxiety was found to be similar in schizophrenia and in schizophrenics having social phobia as a primary diagnosis (Pallanti et al. 2004). In comparison with other schizophrenics, those with social phobia had more suicide attempts of a greater lethality and a lower social adjustment.

Treatment
Small sample studies suggest that Cognitive-Behavioural Therapy (CBT) is an effective intervention compared to a waiting list, as an adjunctive treatment (Kingsep et al. 2003). Some antipsychotic such as clozapine may worsen or induce social anxiety. Eight out of 12 schizophrenic patients with social anxiety were improved by an SSRI, fluoxetine (Pallanti et al. 1999). Although no systematic study is available, there is consensus that social phobia should be treated and that SSRIs are the first line treatment as an add on therapy.

D. Panic attacks

Importance of the problem
Data from the ECA found panic attacks to be frequent (45 %) in patients with schizophrenia. Schizophrenics with panic attacks had elevated rates of coexisting mental disorders, psychotic symptoms and health service utilization (Goodwin et al. 2003). Panic attacks are associated with an increased risk for comorbid alcohol or substance use disorder. In a clinical sample Labbate et al. (1999) found a co-occurrence in 43 % with a higher rate in paranoid schizophrenics. Chen et al. 2001 also found that schizophrenics with panic attacks had more depressive symptoms, greater hostility and a lower level of functioning.

Treatment
Only anecdotal data are available. It could be that neuroleptics not only do not improve panic attacks but sometimes increase them (Argyle, 1990). Arlow et al. (1997) treated 8 patients with CBT with good outcome on panic attacks. In different studies benzodiazepines such as alprazolam prescribed as an add on medication improved panic attacks and also positive and negative symptoms of the patients (Takahashi et al. 1988, Kahn et al; 1988). Two patients treated with nefazodone improved their panic attacks (Joffe et al. 1999). Therefore alprazolam could be proposed as first line treatment and SSRIs as a second line treatment.

E. Post Traumatic Stress Disorder (PTSD)

Importance of the problem
PTSD is highly prevalent in clinical samples, 52 % for Shaw et al. 1997, 46 % for McGorry et al. 1991. Similar results were observed by Neria et al. 2002. Although a causal relationship is far from established, Mueser et al. (1998) found 98 % of exposure to a traumatic event in a sample of 275 patients. Other authors found lower prevalences (Tibbo et al. 2003). Frame & Morrison 2001 also found a high prevalence (67 %) and were able to show that psychotic symptoms and hospitalisation were a relevant contribution to the traumatization of the sample. Therefore the reduction of distress during hospizalization is a fundamental part of the therapeutic strategy. Few systematic guidelines exist for the treatment of this cormorbidity.

Treatment
Almost no systematic study explored the treatment of PTSD in schizophrenics. It is clear that antipsychotics alone are not a treatment of PTSD in schizophrenics, therefore in practice we suggest that the usual treatment could be proposed as add-on therapies.

(Lecrubier)

II. SEDATIVE ANXIOLYTIC TREATMENT IN ACUTE PSYCHOTIC MANIFESTATIONS OF SCHIZOPHRENIA

The treatment of choice for acute schizophrenia is an atypical antipsychotic. This class of medications is well-tolerated in the medium-term and can thus be used as maintenance therapy. In particular, drugs with little sedative effect are desirable in order to optimise functioning and preserve quality of life. Sedation is also undesirable as it may compromise management of negative symptoms. However, in certain patients who present with significant agitation and anxiety, drugs with low sedative potential may not sufficiently attenuate these symptoms even though hallucinations, delusions and other positive treatments are satisfactorily managed. This 'residual' anxiety may interfere with compliance to medication, as well as being distressing to the patient. Two strategies are available to manage anxiety in such patients, namely the use of sedative antipsychotic drugs or the use of adjuvant benzodiazepine therapy.

Sedative antipsychotics, such as thioridazine, pipamperone, melperone, cyamemazine, flupenthixol or levomepromazine can be used as an associated treatment to manage

both overt psychotic symptoms and anxiety (Garay et al. 1995, Meltzer et al. 2001, Squelart et al. 1977). Once the patient is well-controlled, the treatment can be stoped or switched to a non-sedative drug for maintenance therapy. Several of these sedative antipsychotics have been shown to exert anxiolytic effects at low doses in non-psychotic patients and to relieve anxiety satisfactorily in schizophrenic patients at standard antipsychotic doses (Poldinger at al.1984).

A benzodazapine adjuvant to the usual antipsychotic treatment may also help in preventing the development of a full exacerbation (Carpenter et al. 1999). Short-term adjuvant treatment with benzodiazepines can also be useful in managing patients presenting with marked anxiety and agitation (Barbee et al. 1992, Lingjaerde et al. 1991, Wolkowitz et al.1991). The benzodiazepine should be given in combination with non-sedative disinhibitory antipsychotics, such as several of the atypicals. The choice of benzodiazepine should be orientated towards agents with potent anxiolytic action, low propensity for pharmacokinetic drug interactions and a long half-life to provide uninterrupted cover. Benzodiazepine use should be restricted to as short a time as possible in order to prevent the risk of benzodiazepine dependence and rebound anxiety on treatment cessation. By the use of one of these two strategies, severe anxiety associated with acute psychotic episodes can be satisfactorily managed.
(Lecrubier)

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