European Neuropsychopharmacology (2007) 17, 70–77

www.elsevier.com/locate/euroneuro

ECNP consensus meeting. Negative, depressive and cognitive symptoms of schizophrenia. Nice, March 2004☆

S.A. Montgomery *, B. van Zwieten-Boot

PO Box 8751, London W13 8WH, UK

Received 27 April 2006; accepted 25 May 2006

KEYWORDS
Schizophrenia;
Negative symptoms;
Depressive symptoms;
Cognitive symptoms

1. Background

It has long been recognised that patients with a diagnosis of schizophrenia are heterogenous and suffer in varying degrees from distinct symptom complexes which have been categorised as positive symptoms, negative or deficit symptoms, depressive symptoms, and cognitive impairment. These are not regarded as separate disorders but there is evidence that the different symptom complexes or subgroups of schizophrenia respond differently to different medications. The consensus view is that each of these areas represents a legitimate target for investigation and clinicians and patients are entitled to be informed of any evidence of differential response to guide their choice of treatment. Information on differential effects of drugs in subgroups of schizophrenia is of interest to the prescriber and can be presented in any detail of product characteristics such as the summary of product characteristics (SPC) even though these are not necessarily a separate indication.

In Europe, antipsychotic drugs are licensed for the treatment of schizophrenia without further differentiation. However, some licensed treatments have, in addition, indications and labelling for efficacy on various symptom complexes in schizophrenia. Risperidone is indicated in many countries in Europe for the treatment of negative symptoms of schizophrenia and for the treatment of depressive and anxiety symptoms of schizophrenia; olanzapine is licensed for the treatment of depressive symptoms of schizophrenia; amisulpiride is licensed for the treatment of negative symptoms of schizophrenia.

The consensus meeting was convened in order to review the strength of the evidence for the efficacy of different treatments in these various subgroups. The document produced from the meeting offers reasoned advice on suggested trial designs that are thought most likely to produce clearcut evidence for the efficacy of new or existing treatments that may be targeted at the treatment of negative symptoms, depressive symptoms, or cognitive symptoms of schizophrenia. The evidence of efficacy in the particular subgroup would need to be accompanied by evidence that the treatment did not worsen the symptoms in other subgroups including positive symptoms.

☆ On behalf of the Consensus Committee: AC Altamura, T Barnes, S Kasper, Y Lecrubier, SR Marder, HJ Möller, C Tamminga, J Van Ree. Rapporteur: DB Montgomery.

* Corresponding author.
E-mail address: ENP@samontgomery.co.uk (S.A. Montgomery).

0924-977X/$ - see front matter
doi:10.1016/j.euroneuro.2006.05.004

An underlying methodological difficulty in all the areas discussed is how to distinguish the direct primary effects on the symptoms studied from secondary effects associated with improvement in the underlying condition. This question of "pseudospecificity" needs to be considered.

2. Negative symptoms of schizophrenia

The consensus view is that the burden of negative symptoms is large and the need for treatment is great. The presence of residual symptoms makes it particularly difficult to participate in normal social or occupational life and treatments which clearly improve this symptom complex need to be identified and used.

The occurrence of "negative" symptoms such as apathy, lack of volition or motivation as well as the "positive" symptoms of hallucinations and delusions was recognised early. The framework for discussion of positive and negative symptoms was laid out by Bleuler and by Kraepelin though the concept of deficit states had been developed even earlier.

Currently available antipsychotic drugs exert a relatively good effect on the so-called positive symptoms. This is true both for older conventional and the atypical antipsychotics. However, the therapeutic effect of conventional antipsychotics on negative symptoms of schizophrenia appears less consistent. Atypical antipsychotics, on the other hand, appear to have a wider spectrum of action exerting a therapeutic effect on positive and on negative symptoms whether these are classified as primary symptoms or as symptoms arising secondary to the side effects of conventional antipsychotics.

A metanalysis of efficacy studies shows a reasonable effect of antipsychotics compared to placebo on negative symptoms (Leucht et al., 1999). The path analytic approach, used successfully by some investigators (Moller, 1998), shows that some atypical antipsychotics have a direct effect on negative symptoms although this type of analysis may not be acceptable to regulators. In the acute treatment studies the therapeutic effect of atypical antipsychotics is reported to be particularly clearcut in patients with significant negative symptomatology (Tollefson and Sanger, 1997). In controlled long-term treatment studies, where the secondary negative symptoms are no longer prominent, consistent sustained improvements in negative symptoms have been observed with risperidone, olanzapine, ziprasadone and aripiprazole.

2.1. Measuring negative symptoms

Several scales have been developed to quantify the improvements in the positive as well as the negative symptoms of schizophrenia. The most widely known are probably the Scale for Assessment of Positive symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1985;Andreasen, 1989) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989). Opinion is divided as to the relative advantages of these scales; both are regarded as well-established and useful in assessing negative symptoms and both include measures for assessing simultaneously the improvement or lack of deterioration in positive symptoms. Sufficient data from placebo-controlled studies with a variety of treatments are available to confirm the sensitivity to change of both scales.

Two items, allogia and affective flattening, are considered to be the most important both for diagnosis and for registering change with treatment. It may therefore be helpful to focus on these items in any secondary analysis.

The criteria for a meaningful change for a negative symptom responder have not been sufficiently examined but a reduction from baseline to end point in scale score of 30% or more has been suggested as a potentially useful measure.

2.2. Study population

One approach to assessing efficacy in treating negative symptoms has been to investigate the response of negative symptoms in the usual population of schizophrenia patients included in studies, many of whom have enduring positive as well as enduring negative symptoms. This approach has been criticised as being vulnerable to the influence of apparent secondary negative symptoms due to previous extrapyramidal symptoms (EPS); it is also possible that the presence of a high level of positive symptoms and their response to treatment could have secondary effects on the response of negative symptoms.

An alternative approach is to examine the efficacy of treatment on negative symptoms in a population with persistent stable negative symptoms, the so-called enduring negative symptoms. The population thought most likely to provide evidence of efficacy in the treatment of negative symptoms of schizophrenia would be schizophrenia with partially remitted stable symptoms enriched with persisting negative symptoms.

The consensus on the definition of such a population was that patients must have schizophrenia defined on a recognised diagnostic scale such as the DSMIV (A.P.A., 1994). Additionally, if positive symptoms are present their severity should be only at a modest level, with a score of less than 50 on the SAPS or less than 4 on the PANSS positive items. Patients with extrapyramidal symptoms (EPS) should be excluded and only low or modest levels of concomitant depressive symptoms permitted in an ideal population.

Since alogia and affective flattening are regarded as the core items for negative symptoms it is considered helpful if a minimum severity at entry to a study is defined for both items no matter which pivotal scale is used.

It should be possible to generalise from the response in this population with predominant persistent negative symptoms to the treatment of negative symptoms in general. Any further narrowing and restriction of the population studied is likely to make it difficult to generalise from the response observed to the wider population. Defining the study population too narrowly would also make it difficult to recruit sufficient numbers of patients for a viable study.

In the DSMIV TR (A.P.A., 2000) the type of schizophrenia closest to the population defined above is the Residual Type of Schizophrenia (295.60) where there is a) an absence of prominent delusions, hallucinations, disorganised speech or catatonic behaviour and b) there is continuing evidence of the disturbance as indicated by the presence of negative symptoms (i.e. affective flattening, alogia or avolition). The presence of prominent negative symptoms is recognised as a

Table 1 Population suggested for studies on negative symptoms of schizophrenia

1. Partially remitted stable schizophrenia DSM IV
2. Enriched with persisting negative symptoms e.g. SANS 60 or more or the equivalent on the PANSS
3. Modest level of severity of positive symptoms — e.g. SAP<50, PANSS positive items<4 (mild)
4. Modest level of severity on depressive symptoms e.g. MADRS<16
5. Exclude EPS
6. Prior duration of at least 3 months

course specifier in the longitudinal course of schizophrenia providing that at least one year has elapsed since the onset of active phase symptoms (Table 1).

2.3. Trial design

For an unequivocal demonstration of efficacy a comparison against a placebo control is necessary. The preferred design for the demonstration of the efficacy of a treatment as monotherapy would be the conventional double-blind randomised parallel group comparison with placebo.

An alternative approach is the demonstration of superiority of the treatment under investigation compared under the usual double-blind randomised conditions with a licensed treatment for schizophrenia. The demonstration under conditions of fair comparison of superiority over the comparator would be regarded as evidence of efficacy comparable to evidence from a positive comparison to placebo. Some problems associated with this design would need to be taken into account. For example, any EPS attributed to the comparator treatment might make it difficult to separate primary negative symptoms from the secondary negative symptoms due to EPS. A superiority design may well require larger numbers of relatively scarce patients and for logistical reasons the placebo-controlled design may be preferable.

A further alternative design, a non-inferiority study compared with a reference comparator known to be effective in the treatment of negative symptoms, is the least preferred option. Amisulpiride is the only comparator granted a licence for the treatment of negative symptoms based on evidence from placebo-controlled data in a population similar to that identified in Section 2.2. Doubts have been expressed as to whether this comparator has sufficient efficacy to act as a reliable reference. The assay sensitivity of the population chosen cannot be assumed and the non-inferiority design may not therefore provide entirely compelling evidence of efficacy.

2.3.1. Carryover effects from previous treatment

The study population with persistent negative symptoms by definition would be largely under treatment, which would be discontinued and replaced with active treatment or placebo to test efficacy of an agent used in monotherapy. Discontinuation symptoms and effects of the previous treatments may influence the results. It would be preferable to use only those previous treatments where the discontinuation symptoms are known and quantified and to taper the treatment before stopping to reduce discontinuation symptoms. It may be necessary to switch previous treatments to a single treatment to avoid any potential imbalance. The period of potential discontinuation symptoms may need to be examined separately from the rest of the study.

2.3.2. Duration

The study duration should not be too short to miss the effect in slowly responding patients nor so long as to compromise the results by unnecessary dropouts in a placebo-controlled study. Additionally the study should be sufficiently long to assess the possibility of an increase or re-emergence of positive symptoms.

The duration thought likely to demonstrate efficacy with an effective treatment is 12 weeks, but it might indeed be longer.

The effective dose in longer term treatment may not be the same as in acute treatment and this should be taken into account in selecting the dose, which should be justified.

2.3.3. Analysis

The primary outcome, which should be defined in advance, is the change from baseline on the pivotal scale. The analysis should predefine and defend the method of taking account of missing values. The use of responder criteria, which should also be predefined and justified, may help the judgement of clinical relevance. Further support for the clinical relevance of the response seen in the primary analysis can be provided by significant differences registered on the Clinician s global scales (CGI) and on the functional measures considered appropriate.

2.4. Adjunctive treatment using an add-on design

Studies investigating treatments used as an adjunct have the ethical advantage that no patients will be treated with placebo alone and are somewhat easier to conduct. However, the evidence of the efficacy of a treatment as an adjunctive therapy cannot be used to imply its efficacy as monotherapy. For the unequivocal demonstration of efficacy in monotherapy superiority to either placebo or a justified active comparator is required. If an adjunctive design is considered, potential pharmacokinetic and pharmacodynamic interactions will need to be explored and the influence of possible interactions on the results taken into account.

The population investigated in studies with this design is as defined under Section 2.2, the same pivotal scales (SANS, PANSS, etc) and the same outcome measures are appropriate, and the same 12-week study duration is recommended.

In this design patients stabilised on a previous treatment have the treatment augmented under double-blind randomised conditions either with the new treatment under consideration or with matching placebo. The advantage of this design is treatment is not discontinued and the analysis of efficacy should therefore not be prejudiced by the appearance of discontinuation symptoms or the return of the symptoms of schizophrenia. The expected size of effect might be lower than in comparisons of monotherapy and placebo since the comparison is seeking to establish efficacy

over and above that of the active comparator. The clinical relevance of the advantage observed needs to be justified however. The duration chosen, the power calculations and analysis plan, as well as the dose investigated should all be pre-specified.

3. Depressive symptoms of schizophrenia

Estimates of the prevalence of depressive symptoms in patients with schizophrenia vary and range from 25%—60% (Donlon et al., 1976; Knights and Hirsch, 1981; Montgomery, 1979). In older studies investigating treatment with conventional antipsychotics depressive symptoms in schizophrenia appear to be associated with a higher level of social and occupational dysfunction and a generally poorer outcome. There is also evidence that the depressive symptoms in schizophrenia confer a higher risk of suicide (Roy, 1986). The treatment of depressive symptoms in schizophrenia is therefore an important target.

Evidence that the less responsive depressive symptoms are revealed and appear to increase as the positive symptoms subside during treatment with conventional antipsychotics complicates the investigation of efficacy. Studies with a variety of newer agents such as amisulpiride, risperidone, olanzapine and quetiapine have shown potential advantages in the treatment of depressive symptoms associated with schizophrenia in comparison with both placebo and haloperidol. Of these agents only amisulpiride is licensed in some countries in Europe for the treatment of a depressive disorder (dysthymia) although many are licensed for the treatment of mania. Olanzapine and risperidone have the subindication for the treatment of depressive symptoms as part of their licences to treat schizophrenia. The use of atypical antipsychotics either alone or in combination with antidepressants is currently being investigated for the treatment of both bipolar depression and major depressive disorder and the preliminary results are promising. Antidepressants have been used for many years in combination with antipsychotics to treat resistant depression. The data showing the advantage in resistant depression of the combination of olanzapine and fluoxetine or risperidone in combination with citalopram, fluvoxamine or paroxetine compared with SSRI alone provide further support for this practice (Nemeroff, 2005; Tohen et al., 2003).

The use of newer antidepressants in combination with antipsychotics to treat the depressive symptoms, and possibly negative symptoms, of schizophrenia is encouraged by positive results compared to placebo in the studies of augmentation of antipsychotics. The use of agents as add-on therapy to augment the response to antipsychotics of depressive symptoms in schizophrenia appears to be a justified target for development.

3.1. Target population

It is considered that the efficacy of a potential treatment in treating the depressive symptoms of schizophrenia is most likely to be shown in a population enriched with patients suffering sufficient depressive symptoms. A retrospective analysis of a large study of olanzapine compared to haloperidol showed that the advantage of olanzapine was more clearly observed in those patients having a minimum score of 16 on the Montgomery & Asberg Depression Rating Scale (MADRS).

3.1.1. Study population

The population studied should suffer from schizophrenia defined on the usual diagnostic criteria, enriched with depressive symptoms. To ensure sufficient depressive symptoms a minimum score of 18 or more measured on the MADRS or the equivalent on another scale is recommended. The level of depressive symptoms should be sufficiently high to allow testing of efficacy in this subgroup and they should have been present for at least 1 month.

Some concerns were expressed that too high a score on positive symptoms might make it difficult to rate depressive symptoms. It may be therefore be appropriate to limit the severity of positive symptoms to a moderate level. Patients should have clinically prominent depressive symptoms response of these symptoms should be ascertained as a primary effect and not secondary to improvement on positive and/or negative symptoms.

The overlap between depressive and negative symptoms makes for special difficulties. The severity level of non-depressive negative symptoms should be limited in order to provide more convincing data on depressive symptoms alone.

The presence of EPS is a further complication since akinesia may be registered as agitation on the Hamilton Depression Scale (HAMD) (Hamilton, 1967), and this therefore should be taken into account. The level of EPS at entry to the study should be low or absent.

For add-on studies efficacy will probably be assessed best in patients with partially remitted positive symptoms, which includes an enriched population with persistent depressive symptoms that have not responded to previous treatment. The level of EPS should also be controlled in this population. The presence of the depressive symptoms should be assessed and a prior duration of stable depressive symptoms of at least one month is recommended.

In the DSMIV TR the category closest to the population defined for examining efficacy in the depressive symptoms of schizophrenia is Schizoaffective Disorder depressive type (295.70) where a diagnosis of schizophrenia is concurrent with a major depressive episode. It is unclear whether depressive symptoms in schizophrenia and depressive symptoms that are part of schizo-affective disorder respond in the same way and it will be difficult to generalise from symptoms to syndrome or vice versa. Studies carried out exclusively in schizo-affective disorder might lead to an indication for treatment of this disorder (Table 2).

3.2. Design for monotherapy

The demonstration of a difference compared to placebo provides unequivocal evidence of efficacy and placebo-controlled studies are therefore preferred. Since conventional antipsychotics are not thought to improve the depressive symptoms it would be helpful to include a conventional antipsychotic as a comparator in the placebo-controlled study. This will help establish the efficacy of the

Table 2 Population suggested for studies on depressive symptoms in schizophrenia

	Monotherapy studies	Add-on studies
Depressive symptoms	Depressive symptoms	Persistent depressive symptoms
Stability of depression	At least 4 weeks	At least 4 weeks
Minimum severity	MADRS 18 or equivalent	MADRS 18 or equivalent
Positive symptoms	PANSS positive items 4 or less	Partially remitted positive symptoms PANSS positive symptoms 4 or less
EPS	Controlled or absent	Controlled or absent
Negative	Non-depressive negative symptoms low	Non-depressive negative symptoms low
Duration of study	6—8 weeks	6—8 weeks
PK of interaction	Not applicable	Must be tested

new agent in a population where depressive symptoms are not significantly improved by a standard reference medication. A second approach is to demonstrate direct superiority compared with a standard agent. The numbers needed for such a study might well be higher than is usually required in a placebo controlled study.

3.3. Duration and choice of instruments

The study duration for demonstrating efficacy in monotherapy studies and in placebo-controlled add-on studies appears to be consistent with the studies in major depressive disorder, which are generally of at least 6 weeks duration.

A variety of scales specific for the assessment of changes in the depressive symptoms have been applied in studies in schizophrenia and these appear to provide more reliable data than the depressive factor scores on the PANSS or other similar scales. The MADRS and the HAMD have proved sensitive in quantifying the changes in depressive symptoms and the use of the MADRS has provided evidence to support the labelling of olanzapine for the treatment of depressive symptoms in schizophrenia. The use of the conventional depression scales HAMD and MADRS has the advantage that these scales have been widely used in studies in major depression providing a point of reference. The Calgary scale has been developed specifically for assessing the depressive symptoms of schizophrenia and may prove useful.

The choice of scale should be justified, the responder and remission criteria should be pre-specified and defended. For the MADRS and HAMD the same well known criteria used in major depression may be used.

3.4. Add-on design

The aim of an add-on study is to show that the addition of an agent to an existing treatment is effective in significantly reducing depressive symptoms compared with placebo under the usual conditions with a double-blind randomised group comparison design.

The study design thought most likely to establish efficacy is to investigate response to add-on treatment compared to placebo in a population previously treated with a standard treatment whose positive symptoms have remitted or partially remitted but who have persistent depressive symptoms at a certain minimum level of severity. The recommended duration of the study is 6—8 weeks. This type of study cannot be used to imply direct antidepressant efficacy in monotherapy, it establishes only whether add-on treatment is effective. The studies should be able to check for any deleterious increase in positive symptoms.

The level of EPS due to the previous treatment should be as low as possible and the level of non-depressive negative symptoms kept to a minimum. The strategy should be pre-specified for taking into account missing values in the event that there is an imbalance between the test medication and placebo in the number of patients discontinuing in the study. The choice of rating scales and criteria for responder or remission should be defined in advance and are likely to be the same as for the monotherapy studies. Possible pharmacokinetic interaction of the augmenting agent and standard therapy should be investigated, preferably in advance, and also pharmacodynamics particularly in relation to potential side effects. For example combining antipsychotics and SSRIs or SNRIs may lead to increased occurrence of the serotonergic syndrome.

4. Cognitive symptoms in schizophrenia

Schizophrenia was perceived by early authorities as a cognitive disorder and the concept of dementia praecox reflects the view that early psychosis predisposes the patient to develop dementia (Kraepelin, 1999). The functional outcome of schizophrenia has remained more or less constant over the last century despite the discovery and introduction of effective treatments for schizophrenia (Hegarty et al., 1994; Tsuang et al., 1979). The ability to acquire and retain social and vocational skills requires intact cognitive function and the poor performance of treatments aimed at treating positive symptoms in influencing vocational outcome has been attributed partially to their failure to improve cognitive symptoms. The finding that some 85% of stable outpatients with minimal psychotic symptoms show significant cognitive impairment highlights the need for treatments for the cognitive symptoms of schizophrenia.

Patients with schizophrenia may suffer from a wide range of cognitive deficits which include attention, executive function (problem solving), working memory, secondary memory, verbal memory, and speed of processing (Saykin et al., 1994). Impairment in these domains has been reported in first episode schizophrenia although impairment in executive function and verbal memory is reported to worsen with the passage of time. Some 85% of patients with schizophrenia are reported to have some cognitive deficits, mostly at a moderate to severe range (Meltzer and McGurk, 1999). Cognitive deficits in executive function, working

memory, and attention appear to be a better predictor of poor social and occupational functioning than positive symptoms (Green, 1996; McGurk and Meltzer, 2000).

Secondary cognitive deficits such as impairment of learning and memory can appear in association with treatment with the anticholinergic agents used to treat EPS (Spohn and Strauss, 1989).

There is increasing evidence that while conventional antipsychotics effectively control the positive symptoms of schizophrenia they do not appear to produce consistent improvements in attention, vigilance, memory, or executive function. In contrast newer antipsychotics, for example clozapine, risperidone, quetiapine, ziprasidone and aripiprazole, are thought to improve cognitive function in schizophrenia (Harvey and Keefe, 2001; Meltzer, 1997). The identification of the specific benefits of different treatments has not yet been established.

4.1. Measures of efficacy

There is a wide range of tests for different aspects of cognitive function which cover multiple aspects of attention, memory, fluency and reasoning. The specificity and sensitivity of some of these tests has not yet been assessed let alone subjected to placebo-controlled efficacy testing so that the choice of scales is not easy. The choice of neurocognitive tests should take into account their relevance for the domains impaired in schizophrenia, their reliability, their relationship to a functional outcome, their sensitivity to treatment and their practicability and tolerability in a placebo-controlled setting.

The NIMH initiative Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) examined potential cognitive targets for investigation and concluded that tests are needed in the separate domains of speed of processing, attention, working memory (verbal, learning and visual), reasoning and problem solving, and social cognition. The consensus view is that there is substantial support for the identification of these domains for the testing of efficacy.

Following assessment of a variety of scales addressing these different domains for validity test retest reliability, utility as a repeated measure, relationships to functional outcome and practicality and tolerability, MATRICS identified potential tests for use in add-on studies, available at http://www.matrics.ucla.edu/matrics-recommendations.

It is claimed that a battery including all the recommended tests would take just over an hour to administer. However, this needs to be tested in different settings. The length of contact time required by such a test battery would be expected to increase non-specific response.

It is probable that the tests found to be useful in augmentation studies will also be useful in monotherapy studies but this question has not yet been addressed.

There are as yet insufficient data on any particular measure to conclude whether they are useful or practicable in schizophrenia, and whether the individual measures are sufficiently sensitive to register improvement if a treatment is effective. There are considerable reservations as to whether these tests would be sensitive within the constraints of a clinical study.

4.2. Pivotal measures

There was agreement that the cognitive tests or battery of tests must be pre-specified and that a single pivotal measure must be identified in advance. The domains investigated should include the seven domains identified by the MATRICS group which were approved by the consensus meeting. It is unclear whether a significant difference from placebo should be achieved in all 7 domains specified or merely in some domains. The consensus view was that a single composite weighted endpoint using all domains is most likely to be useful for assessing improvement in cognitive deficits. Both the tests and the single composite endpoint should be justified in advance and the clinical relevance of the efficacy shown on the cognitive tests should also be established. The consensus view was that the cognitive measures on their own would not be sufficient but that positive results should to be supported by significant changes in functional or social measures.

4.3. Trial design

Potential efficacy in cognitive symptoms of schizophrenia can be investigated in monotherapy or where an agent is used as an add-on to existing treatment.

4.3.1. Monotherapy

To establish the efficacy of an agent as monotherapy for the treatment of cognitive symptoms in schizophrenia efficacy in the treatment of positive symptoms should be shown whilst at the same time showing that the agent does not induce negative or depressive symptoms. To show unequivocal efficacy for monotherapy a positive result from the usual double-blind randomised controlled study compared with placebo would be required. The demonstration, under conditions of fair comparison, of a significant advantage compared to a conventional treatment for schizophrenia would be acceptable evidence of efficacy but the possibility that the particular comparator used might induce cognitive deficits would need to be addressed. The potential rebound and carry-over effects of previous treatments prior to being randomised to drug or placebo also need to be taken into account.

Since the measures of efficacy, the potential potency of the test agent, and the appropriateness of the trial design are unknown it is difficult to predict the duration of treatment needed in such a placebo-controlled study. It was considered unlikely that efficacy would be shown in less than 12 weeks and possibly an even longer duration might be needed, particularly if supporting evidence from functional and social changes were required.

The preferred trial design would be a 3-way design including placebo and a conventional comparator in order to show the level of improvement which could be expected with conventional treatment.

4.3.2. Add-on treatment

A number of agents are being developed which may be effective in improving cognitive function in schizophrenia when used to augment existing treatments. The preferred design to test the efficacy of an add-on agent is a double-

blind randomised group comparison of response to the add-on agent plus standard therapy compared with placebo plus standard therapy. A significant positive study result cannot imply that the agent is effective as monotherapy. A significant difference between augmentation of standard treatment compared with standard treatment clearly implies that the standard therapy is less adequate and that the add-on therapy is needed.

The potential for pharmacokinetic interactions with the treatments being augmented should be investigated. Similarly the potential of the augmented treatments to impair or worsen cognitive function, depression, or the underlying schizophrenia should also be established. Concomitant treatment with anticholinergic compounds that are known to impair cognitive function should be excluded in these studies. As with the monotherapy design a firm conclusion on study duration is not possible from current data but it is considered unlikely that a significant difference would be shown in less than 3 months. Efficacy shown on a pre-specified cognitive composite weighted test should be supported by significant advantages in functional or social measures in order to demonstrate that the effect observed is clinically relevant. The studies should establish that there is no increase in EPS or other untoward symptoms and should quantify the expected increase in the side effect burden.

4.4. Population studied

The population studied should meet internationally recognised diagnostic criteria for schizophrenia. However, the severity of cognitive impairment that would be appropriate for studies has not been determined. The tests are likely to be more sensitive if a population enriched with patients suffering with cognitive impairment is investigated but the techniques for achieving enrichment have yet to be determined.

There are understandable concerns that the presence of positive symptoms might interfere with the conduct of some of these cognitive tests and it may be necessary therefore to limit the severity of the positive symptoms. Likewise, some of the domains, e.g. memory, attention and speed of processing, are thought to be impaired in patients with depressive symptoms of schizophrenia. In order to distinguish between a direct effect on cognitive symptoms and improvement in cognitive symptoms due to a reduction in depressive symptoms during treatment it should be helpful to limit the severity of the depressive symptoms present in the population of schizophrenia to be tested.

4.5. Clinical relevance

To date no treatment has been licensed for the treatment of cognitive symptoms of schizophrenia but the inclusion of a comparator treatment can give some indication of the relative effect of an agent compared to that seen during standard available treatment. It is difficult to make recommendations on the clinical relevance of significant changes observed on cognitive tests. One suggestion is to estimate the general functional improvement observed on a clinically relevant scale. Since it is claimed that cognitive dysfunction (particularly attention, reasoning and working memory) is a predictor of poor social and occupational functioning it would seem reasonable to use functional or disability scales to document improvement and help understand the clinical relevance of the changes on cognitive scales.

4.6. Long-term treatment

It is unclear whether cognitive improvements observed will relapse in a predictable way when treatment is discontinued. Many suspect that response to successful treatment in an acute study will be followed by further gains if treatment is continued and relapse prevention studies with randomisation of responders to continued treatment or discontinuation on to placebo may therefore be difficult to interpret.

The alternative method of investigating long-term efficacy would be to focus on a potential superiority over a standard comparator in improvement in cognitive function over the long-term under the usual randomised double-blind controlled conditions. Alternatively the efficacy of the test treatment could be compared with both placebo and a standard comparator over a longer duration of, say, 6 months which would be especially useful to assess the effect on positive symptoms in the longer term.

5. Conclusion

The negative, depressive and cognitive symptom complexes or subgroups of schizophrenia are considered important and legitimate targets for investigation and treatment.

The methodologies for investigating potential treatments in each area are outlined in the document. Substantial data from studies in investigating negative and depressive symptoms in schizophrenia are now available and the conclusions reached are probably justified. The investigation of cognitive symptoms of schizophrenia is less well advanced and conclusions on the appropriate methodology must be regarded as more tentative.

References

A.P.A., 1994. Diagnostic and Statistical Manual of Mental Disorders DSM-IV. American Psychiatric Association, Washington.

A.P.A., 2000. Diagnostic Criteria from DSM-IV-TR. American Psychiatric Association, Washington.

Andreasen, N.C., 1985. Positive vs. negative schizophrenia: a critical evaluation. Schizophr. Bull. 11 (3), 380–389.

Andreasen, N.C., 1989. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br. J. Psychiatry (Suppl no. 7), 49–58.

Donlon, P.T., Rada, R.T., Arora, K.K., 1976. Depression and the reintegration phase of acute schizophrenia. Am. J. Psychiatry 133, 1265–1268.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153 (3), 321–330.

Hamilton, M., 1967. Development of rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.

Harvey, P.D., Keefe, R.S., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry 158 (2), 176–184.

Hegarty, J.D., Baldessarini, R.J., Tohen, M., Waternaux, C., Oepen, G., 1994. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am. J. Psychiatry 151 (10), 1409–1416.

Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The positive and negative syndrome scale (PANSS): rationale and standardization. Br. J. Psychiatry 155 (Suppl. 7), 59–65.

Knights, A., Hirsch, S.R., 1981. Revealed depression and drug treatment for schizophrenic. Arch. Gen. Psychiatry 38, 800–811.

Kraepelin, E., 1999. Dementia praecox and paraphrenia. Livingstone, Edinburgh.

Leucht, S., Pitschel-Walz, G., Abraham, D., Kissling, W., 1999. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr. Res. 35 (1), 51–68.

McGurk, S.R., Meltzer, H.Y., 2000. The role of cognition in vocational functioning in schizophrenia. Schizophr. Res. 45 (3), 175–184.

Meltzer, H.Y., 1997. Treatment-resistant schizophrenia — the role of clozapine. Curr. Med. Res. Opin. 14 (1), 1–20.

Meltzer, H.Y., McGurk, S.R., 1999. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr. Bull. 25 (2), 233–255.

Moller, H.J., 1998. Novel antipsychotics and negative symptoms. Int. Clin. Psychopharmacol. 13 (Suppl 3), S43–S47.

Montgomery, S.A., 1979. Depressive symptoms in acute schizophrenia. Prog. Neuropsychopharmacol. 3, 429–433.

Nemeroff, C.B., 2005. Use of atypical antipsychotics in refractory depression and anxiety. J. Clin. Psychiatry 66 (Suppl 8), 13–21.

Roy, A., 1986. Depression, attempted suicide, and suicide in patients with chronic schizophrenia. Psychiatr. Clin. North Am. 9, 193–206.

Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch. Gen. Psychiatry 51 (2), 124–131.

Spohn, H.E., Strauss, M.E., 1989. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. J. Abnorm. Psychology 98 (4), 367–380.

Tohen, M., Vieta, E., Calabrese, J., Ketter, T.A., Sachs, G., Bowden, C., Mitchell, P.B., Centorrino, F., Risser, R., Baker, R.W., Evans, A.R., Beymer, K., Dube, S., Tollefson, G.D., Breier, A., 2003. Efficacy of olanzapine and olanzapine—fluoxetine combination in the treatment of bipolar I depression. Arch. Gen. Psychiatry 60 (no. 11), 1079–1088.

Tollefson, G.D., Sanger, T.M., 1997. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am. J. Psychiatry 154 (4), 466–474.

Tsuang, M.T., Woolson, R.F., Fleming, J.A., 1979. Long-term outcome of major psychoses: I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. Arch. Gen. Psychiatry 36 (12), 1295–1301.