Pfizer Inc.

Pfizer-SAT2. From patients to people – new goals in schizophrenia management

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Pfizer-SAT2-1

ZIPRASIDONE: FROM RECEPTOR PROFILE TO PATIENT OUTCOMES — A REVIEW OF SHORT-TERM EFFICACY STUDIES

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Ziprasidone is a novel antipsychotic agent with a unique combination of receptor affinities. It has a high D_2 affinity, associated with antipsychotic efficacy, but a much greater affinity for 5-HT_{2A} receptors, which may predict efficacy in negative symptoms and a low extrapyramidal symptom (EPS) liability compared with traditional antipsychotics. In contrast to olanzapine and risperidone, ziprasidone exhibits potent 5-HT_{1A} agonism, which may be linked to efficacy in symptoms of anxiety and depression. Ziprasidone also differs from other agents in its potent 5-HT_{1D} receptor agonism, an effect also associated with anxiolytic and antidepressant activity. Ziprasidone also inhibits serotonin and noradrenaline reuptake, an effect associated with antidepressant activity and which ziprasidone shares with conventional antidepressants such as amitriptyline. Other features of ziprasidone's receptor profile include modest histaminergic, α_1-adrenergic activity, and negligible muscarinic receptor activity, suggestive of limited potential for sedation, orthostatic hypotension, and anticholinergic side-effects.

The clinical efficacy and tolerability of ziprasidone has been demonstrated in clinical trials. In 4- and 6-week double-blind studies, ziprasidone was shown to be clinically significantly more effective than placebo in reducing positive symptoms, negative symptoms, and depressive symptoms in patients with acute exacerbation of schizophrenia or schizoaffective disorder. Significant, dose-related improvements from baseline symptom scores on measures of positive and negative symptoms were achieved with ziprasidone 80–160 mg daily from week 1 in a 6-week placebo-controlled study. Furthermore, a subset of patients with depressive symptoms (Montgomery-Åsberg Depression Rating Scale score $\geq$ 14) showed significant improvement in depressive symptoms after 6 weeks' treatment with ziprasidone 160 mg daily. Ziprasidone 160 mg daily was shown to be as effective as haloperidol 15 mg daily with superior tolerability in a 4-week, double-blind, haloperidol controlled study.

Ziprasidone is the first of the new antipsychotics to be developed in an intramuscular (IM) formulation. In clinical studies in acutely agitated patients, ziprasidone 5, 10 and 20 mg IM (up to qid) for up to 3 days was shown to be effective in rapidly controlling acute agitation and well tolerated. Ziprasidone IM was associated with fewer movement disorders than flexible-dose haloperidol IM. The transition from IM to oral ziprasidone was made smoothly with maintained symptom control and tolerability.

Pfizer-SAT2-2

THE IMPACT OF SIDE EFFECTS — PATIENT, FAMILY AND PHYSICIAN CONCERNS

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The side-effects of antipsychotic drugs pose different but overlapping concerns for the patient, family and physician. For the patient and his/her family, it is the side-effects that stigmatize and diminish quality of life that are of prime concern. These include physical effects, such as movement disorders, weight gain and sexual dysfunction. Traditionally, the primary side-effect concerns of the psychiatrist have been movement disorders, particularly acute extrapyramidal symtptoms (EPS) and tardive dyskinesia. Other side-effects have had secondary importance. This emphasis is changing, however, with the availability of newer antipsychotics which carry a lower risk of EPS. As the relative importance of EPS becomes less, other side-effects are becoming increasingly recognized as important and potentially treatment-limiting.

From the physician's perspective, any side-effect that limits patient satisfaction with treatment can have a negative impact on compliance, a major factor in treatment failure and relapse. Data have shown that side-effects that diminish self-esteem and subjective wellbeing, such as weight gain and sexual dysfunction, are generally the most distressing to patients, and among the most likely to lead to non-compliance. Weight gain is also important as a risk factor for obesity-related illnesses, which increase morbidity and mortality. Adverse effects such as sedation and cognitive impairment, which affect functioning, may also impact on compliance. Adverse effects are only one factor in the multifactorial problem of non-compliance, however. The doctor-patient relationship, the psychosocial background of the patient and the information available to them, are among the many other factors that need to be taken into account when discussing this critical issue.

Although sometimes artificially categorized as 'atypical', the novel antipsychotics have strikingly different pharmacological profiles and, consequently, different clinical side-effect risks. The pharmacological management of patients suffering from schizophrenic disorders has become increasingly guided by side-effects, and the challenge is still to find the right drug for the right patient. Comparing the risk-benefit ratios of the new antipsychotics is difficult, as very few head-to-head comparisons are available. Post-hoc analyses of clinical trials with the various drugs can be misleading, as studies tend to have considerable methodological differences in side effect assessments. Inferences from such studies should therefore be made very cautiously. Well-designed Phase IV studies allowing direct comparisons of novel antipsychotics will be needed to make evidence-based clinical recommendations.

Pfizer-SAT2-3

A BASIS FOR OPTIMISM — THE IMPLICATIONS OF LONG-TERM TREATMENT

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Studies have shown that long-term treatment of schizophrenia can cut relapse rates associated with schizophrenia and facilitate the rehabilitation of the patient into society. The 2-year Treatment Strategies in Schizophrenia (TSS) study, which evaluated continuous versus intermittent maintenance therapy regimens, showed that relapse rates were lowest in patients receiving continuous antipsychotic treatment and highest among patients receiving treatment only during symptomatic phases.

Traditionally, antipsychotic therapy is associated with high rates of non-compliance - estimates suggest that about two-thirds of patients fail to take their medication regularly. As indicated by the TSS study, compliance with continuous treatment is essential in order to reduce the risk of relapse and facilitate the rehabilitation of the patient into society. It is hoped that the new antipsychotics will enhance compliance with the long-term treatment plan through their improved tolerability profiles in comparison with traditional agents. If the benefits of better tolerability and efficacy across the wider symptom spectrum seen with newer antipsychotics can be

sustained over long-term treatment, this may facilitate application of psychoeducational treatments, which have been shown to enhance the social and vocational rehabilitation of some patients.

There are two models used to evaluate the long-term effectiveness of new antipsychotics: (1) comparison against traditional agents, and (2) multiple dose comparisons. Ziprasidone, a new antipsychotic, has been evaluated in a 52-week double-blind, placebo-controlled, dose-comparison study in 294 adults hospitalized with chronic, stable schizophrenia, the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. The results of this study support a role for ziprasidone in the maintenance treatment of schizophrenia. Ziprasidone was associated with a significant reduction in the probability of symptom exacerbation compared with placebo. There were dose-related improvements in measures of positive and negative symptoms and overall psychological functioning, which were significantly greater than placebo. The improvement in negative symptoms seen with ziprasidone was continuous over the 1-year time course. A low incidence of side-effects associated with non-compliance - extrapyramidal symptoms (EPS), weight gain and sexual dysfunction - indicates that tolerability-related non-compliance rates may be low with long-term use.

Further comparative studies are needed to evaluate the long-term effectiveness of newer antipsychotics and their potential to contribute to enhanced treatment outcomes.

Pfizer-SAT2-4

ACHIEVING EFFECTIVE TREATMENT ALLIANCES — INTRODUCING A NEW PATIENT, CARER AND CARE TEAM PROGRAMME

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Optimal management of schizophrenia requires an integrated approach combining medication and appropriate psychoeducational support for the patient and his or her family. Current limitations to the delivery of integrated management include a lack of care team time and resources and the lack of understanding of schizophrenia and the benefits of continued medication among patients and carers, which results in non-compliance wth psychoeducational treatments.

A new programme designed to address some of these problems has been developed. The *Alliance Programme* is an integrated resource package designed to build a new alliance between patient, carer and care team. It comprises information and education for patients and carers in interactive, modular format, and resources and training for the care team to support the implementation of a psychoeducational programme. The *Alliance Programme* responds to the real needs of clinical practice identified by patients, carers and care teams in an international survey and, uniquely, has proactively involved patients and their families closely in its development. The information for patients and carers encourages interaction between all members of the care programme - patient and carer and care team - and is designed to increase understanding of schizophrenia and its treatment and to encourage self-help measures. Importantly, the *Alliance Programme* is adaptable to the needs of the care team and their clients, complementing the team's current approaches.

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