QUTAN (Quetiapine)

Available as Quetiapine plain tablets: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg

QUTAN SR (Quetiapine sustained release)

Available as Quetiapine sustained release formulation: QUTAN SR: 100 mg, 200 mg, 300 mg, 400 mg

(1) Indications (for elderly):

- Bipolar disorder (depressive episodes along with bipolar disorder, manic episodes of bipolar disorder [alone or adjuvant], maintenance treatment of bipolar disorder as adjuvant)
- Schizophrenia

(2) Recent trials:

Abstract 1

Quetiapine for the treatment of bipolar mania in older adults

Sajatovic M, Calabrese JR, Mullen J.
Bipolar Disord 2008: 10: 662–671.

Objectives: A post hoc analysis of pooled data from two quetiapine monotherapy clinical trials was conducted to evaluate the efficacy and tolerability of quetiapine therapy (twice daily, 400–800 mg/day) among bipolar manic adults aged 55 years and older. The primary efficacy endpoint was the change from baseline in Young Mania Rating Scale (YMRS) total score at Day 21. A secondary endpoint was change from baseline in YMRS score at Day 84.

Methods: A total of 407 patients made up the safety population, consisting of 59 older adults (aged ≥55 years) and 348 younger adults. A total of 403 patients made up the efficacy population, consisting of 59 older adults and 344 younger adults. Efficacy outcomes were analyzed using covariance models (ANCOVA); descriptive statistics are presented for safety outcomes.

Results: Both older and younger individuals treated with quetiapine had significant improvement from baseline on YMRS scores compared with placebo-treated patients. The older adult group demonstrated a sustained reduction in YMRS score compared with placebo that was apparent by Day 4 of treatment. For the quetiapine treatment groups, the

most common adverse effects (at a frequency ≥10%) were dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness in older adults, and dry mouth, somnolence, and insomnia in younger adults. For the placebo treatment groups, insomnia was the most common adverse event in both older and younger adults.

Conclusions: This secondary analysis suggests that quetiapine represents a potentially useful treatment option among older adults with bipolar I mania. Studies with a primary focus of geriatric bipolar mania, and including larger patient numbers, are needed to confirm these findings.

Abstract 2

The efficacy and safety of quetiapine for treatment of geriatric psychosis

Hung Yang C, Tsai SJ, Hwang JP.
Journal of Psychopharmacology 2005;1996 (6):661-666.

Quetiapine, an atypical antipsychotic, is effective for psychosis in younger patients, with limited adverse effects reported. This open-label naturalistic study was conducted to assess the 4-week efficacy and safety of quetiapine for treatment of geriatric psychosis. Clinical efficacy was evaluated using the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression Improvement (CGI-I) instruments before and after 4 weeks of quetiapine treatment. The sample population consisted of 100 geropsychiatric inpatients with psychosis, with the therapeutic evaluation completed by 91. Eighty-one of these 91 patients (89.0%) experienced mild-to-substantial improvement, as determined from the CGI-I. Further, a mean reduction in BPRS score of 39.5% (from baseline) was also determined. The mean daily dose of quetiapine for the fourth week was 276.1 177.2mg/day (range 50-800). Higher quetiapine dosages were administered for patients with functional psychoses compared to an analogous group with organic mental disorders. The most common adverse effects were somnolence (30.0%), lower-limb weakness (28.0%) and dizziness (27.0%). Body weight and fasting triglyceride were significantly elevated after quetiapine treatment (2.2% and 8.9% from baseline, respectively). **Based on the results of this study, it appears that quetiapine is an efficacious and safe treatment for geriatric inpatients with psychosis,** however, there is a wide dosing range and optimal dosage is diagnosis-dependent.

Abstract 3

Demonstration of an anti-oxidative stress mechanism of quetiapine: implications for the treatment of Alzheimer's disease.

Xu H, Wang H, Zhuang L, Yan B, et al.

FEBS J. 2008 Jul;275(14):3718-28.

We have shown that quetiapine, a new antipsychotic drug, protects cultured cells against oxidative stress-related cytotoxicities induced by amyloid beta (Abeta)25-35, and that quetiapine prevents memory impairment and decreases Abeta plaques in the brains of amyloid precursor protein (APP)/presenilin-1 (PS-1) double-mutant mice. The aim of this study was to understand why quetiapine has these protective effects. Because the cytotoxicity of both Abeta(25-35) and Abeta(1-40) requires fibril formation, our first experiments determined the effect of quetiapine on Abeta(25-35) aggregation. Quetiapine inhibited Abeta(25-35) aggregation in cell-free aqueous solutions and blocked the fibrillar aggregation of Abeta(25-35), as observed under an electron microscope. We then investigated why quetiapine inhibits Abeta(25-35) aggregation. During the aggregation of Abeta(25-35), a hydroxyl radical (OH*) was released, which in turn amplified Abeta(25-35) aggregation. Quetiapine blocked OH*-induced Abeta(25-35) aggregation and scavenged the OH* produced in the Fenton system and in the Abeta(25-35) solution, as analyzed using electron paramagnetic resonance spectroscopy. Furthermore, new compounds formed by quetiapine and OH* were observed in MS analysis. Finally, we applied Abeta(25-35) to PC12 cells to observe the effect of quetiapine on living cells. Abeta(25-35) increased levels of intracellular reactive oxygen species and calcium in PC12 cells and caused cell death, but these toxic effects were prevented by quetiapine. These results demonstrate an **anti-oxidative stress mechanism of quetiapine, which contributes to its protective effects observed in our previous studies and explains the effectiveness of this drug for Alzheimer's disease patients with psychiatric and behavioral complications.**

Abstract 4

Expert opinion on the management of behavioural and psychological symptoms of dementia (BPSD) and investigation into prescribing practices in the UK.

Bishara D, Taylor D, Howard RJ, Abdel-Tawab R.
Int J Geriatr Psychiatry. 2009 Jan 20. [Epub ahead of print]

BACKGROUND: The management of Behavioural and Psychological Symptoms of Dementia (BPSD) has been the subject of considerable debate over the last few years in view of the poor evidence base for pharmacological agents and concerns about their safety.

OBJECTIVES: This study sought to obtain expert opinion on the management of BPSD and to investigate current prescribing practices in the UK.

METHOD: A total of 166 expert opinion surveys were emailed to UK consultants in Old Age Psychiatry asking them to rate the appropriateness of psychotropics in different aspects of BPSD. A service evaluation was also carried out in 8 UK centres to investigate prescribing patterns.

RESULTS: Overall, 59 consultants returned completed questionnaires, a response rate of 35%. Results revealed that experts rated quetiapine as the most appropriate agent for all BPSD followed by acetylcholinesterase inhibitors for psychotic symptoms, benzodiazepines for agitation or aggression and trazodone for behavioural symptoms such as disinhibition. The service evaluations showed that benzodiazepines were most frequently prescribed for BPSD.

CONCLUSIONS: Although quetiapine was judged by experts to be the most appropriate agent for BPSD, it appears that in clinical practice benzodiazepines are most often used to manage these symptoms. Evidence from both studies show wide inconsistencies in prescribing trends.

Abstract 5

Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study.

Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA.
Curr Alzheimer Res. 2007 Feb;4(1):81-93.

In this 10-week, double-blind, fixed-dose study, elderly institutionalized patients with dementia and agitation were randomized (3:3:2) to quetiapine 200mg/day, 100mg/day, or placebo. The primary endpoint was change in Positive and Negative Syndrome Scale (PANSS)-Excitement Component (EC) scores at endpoint, analysed using last observation carried forward (LOCF) and observed cases (OC) approaches. Other efficacy measures were the Clinical Global Impression of Change (CGI-C), and response rates (percentage with > or =40% reduction [PANSS-EC]; "much" or "very much improved" [CGI-C]), Neuropsychiatric Inventory-Nursing Home version (NPI-NH), and Cohen-Mansfield Agitation Inventory (CMAI). The key safety measure was incidence of adverse events; change in Mini-Mental State Examination (MMSE) was also assessed. Baseline characteristics of 333 participants (quetiapine 200mg/day, n=117; quetiapine 100mg/day, n=124; placebo, n=92) and completion rates (63-65%) were comparable among groups. Compared with placebo, quetiapine 200mg/day was associated with clinically greater improvements in PANSS-EC (LOCF, p=0.065; OC, p=0.014 [ANCOVA]), CGI-C (LOCF, p=0.017; OC, p=0.002 [ANOVA]), and CGI-C response rates (LOCF, p=0.002; OC, p<0.001 [Chi-square test]). Quetiapine 100mg/day did not differentiate from placebo on these measures. There were no between-group differences in NPI-NH or CMAI. Incidences of cerebrovascular adverse events, postural hypotension, and falls were similar among groups. MMSE did not change in any group. Mortality was numerically higher in the quetiapine groups; rates were not statistically different from placebo. The results of this study suggest **that quetiapine 200mg/day was effective and well-tolerated for treating agitation associated with dementia.** However, caution should be exercised given the concerns regarding increased mortality with atypical antipsychotics in this vulnerable patient population.

Abstract 6

Quetiapine effective in treatment of inappropriate sexual behavior of lewy body disease with predominant frontal lobe signs.

Prakash R, Pathak A, Munda S, Bagati D.

Am J Alzheimers Dis Other Demen. 2009 Apr-May;24(2):136-40. Epub 2009 Jan 7.

Dementia of Lewy body disease is the second most common degenerative cause of dementia after Alzheimer's disease, among all the dementias. The core features are a progressive dementia, fluctuations in cognitive functions, visual hallucinations, and spontaneous parkinsonism. Rapid eye movement sleep behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia are other suggestive features. Behavioral abnormalities are commonly present in the form of aggressive behavior, irritability, and uninhibited behaviors. These are mostly seen in the advanced stages of dementia. However, inappropriate sexual behavior is uncommonly seen in such cases. Three types of inappropriate sexual behaviors commonly found in cases of dementia are sex talks, sexual acts, and implied sexual acts. Such inappropriate sexual behaviors have not been described adequately in dementia of Lewy body disease. We report **inappropriate sexual behaviors in a case of dementia of Lewy body disease, which improved rapidly after treatment with quetiapine.**

Abstract 7

Quetiapine versus risperidone in elderly patients with behavioural and psychological symptoms of dementia: efficacy, safety and cognitive function.

Rainer M, Haushofer M, Pfolz H, Struhal C, Wick W.
Eur Psychiatry. 2007 Sep;22(6):395-403. Epub 2007 May 4.

OBJECTIVE: In this study we directly compared the efficacy and tolerability of the atypical antipsychotics quetiapine and risperidone in elderly patients with dementia and symptoms of disturbed perception, thought content, mood or behaviour (behavioural and psychological symptoms of dementia-BPSD).

METHODS: We conducted an 8-week, rater-blinded, randomised study of 72 outpatients (55-85 years) with BPSD (assessed by NPI baseline score), who received flexibly-dosed quetiapine (50-400 mg/day) or risperidone (0.5-2 mg/day). Primary efficacy measure: Neuropsychiatric Inventory (NPI) Parts 1 and 2; secondary efficacy measures: Clinical Global Impression (CGI), Cohen-Mansfield Agitation Inventory (CMAI), Mini-Mental State Examination (MMSE), Age-adjusted concentration test (AKT). Safety evaluations included the incidence of extrapyramidal symptoms (EPS) and adverse events (AEs).

RESULTS: Sixty-nine of 72 patients were evaluable for efficacy (72 were evaluated for safety), 4 patients discontinued (3 due to AEs: quetiapine 2, risperidone 1; 1 lost to follow-up). Sixty-five patients received quetiapine (n=34; mean dose 77+/-40 mg/day) or risperidone (n=31; mean dose 0.9+/-0.3 mg/day). There was no significant difference between treatments on NPI scores; within treatment groups, NPI scores decreased significantly from baseline to Week 8 (P<or=0.05 vs. baseline). Most patients (quetiapine arm 67.6%, risperidone arm 71.0%) experienced clinical improvement (CGI-Improvement scores); both agents reduced agitation (CMAI scores); and there was no cognitive impairment (MMSE and AKT scores). There were no significant differences between treatments in any safety measures, including EPS. Four patients experienced serious AEs (quetiapine arm 3; risperidone arm 1); none were considered treatment-related by the study investigator. There were no cerebrovascular AEs or deaths.

CONCLUSIONS: **Quetiapine or risperidone, at low doses, were equally effective and generally well tolerated (including no cognitive impairment) in the treatment of BPSD in elderly patients.**

(3) Dosage in elderly:

As with other antipsychotics, QUTAN should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on QUTAN 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients. (doses up to 750 mg/day has been studied in younger patients)

There should be lower starting dose, slower titration and careful monitoring during initial dosing period in elderly. This is due to decreased clearance, increased chances of pharmacodynamic response and increased risk of orthostatic hypotension in elderly.

(4) Common side effects:

Common side effects are sedation, somnolence, dry mouth, dizziness and orthostatic hypotension. Quetiapine may cause abdominal pain, constipation, diminished movement, excessive muscle tone, headache, indigestion, nasal inflammation, neck rigidity, rapid heartbeat, rash, tremor, uncontrollable movements and weakness.