Management of Depressive Symptoms in Schizophrenia: A Pooled, Post Hoc Analysis From the Asenapine Development Program

David J. Castle [1], Jens-Kristian Slott Jensen [2]

Abstract

Background: Although depressive symptoms are a frequently occurring phenomenon in schizophrenia, effective treatments remain an area of clinical need. **Objective:** To assess the benefit of short-term treatment with the atypical antipsychotic asenapine versus placebo on depressive symptoms in patients with acute schizophrenia in an exacerbated state. **Methods:** Data were pooled from intent-to-treat (ITT) populations of three 6-week, randomized controlled studies with fixed doses of asenapine (ASE; n=427), olanzapine (OLA; n=82), risperidone (RIS; n=54), haloperidol (HAL; n=97), or placebo (PLA; n=254). Change from baseline Calgary Depression Scale for Schizophrenia (CDSS) total score and individual item scores were assessed at Day 21 and Day 42 in the total patient population (n=914), and in patients presenting with a CDSS total score of ≥6 at baseline (n=248). Mixed model repeated measures (MMRM) analyses were performed on patient data. **Results:** The observed change from baseline in CDSS total score was significantly larger with ASE—compared to PLA—at both Day 21 ($p<0.05$) and Day 42 ($p<0.01$) for the total patient population group, and at Day 21 ($p<0.05$) in patients with baseline CDSS total score ≥6. For both populations, there was a significant change from baseline in the CDSS depression item score with ASE—compared to PLA—at Day 21 ($p<0.01$, all patient population; $p<0.05$, patients with baseline CDSS ≥6), and at Day 42 ($p<0.01$) in the all patient population. Statistically significant changes from baseline, in favor of ASE versus PLA, were also observed in other individual CDSS item scores including hopelessness ($p<0.05$, Day 21, patients with baseline CDSS ≥6), self-depreciation ($p<0.05$, Day 42, all patient population), guilty ideas of reference ($p<0.01$, Day 42, all patient population), pathological guilt ($p<0.01$, Day 21, all patient population; $p<0.05$, Day 21 and Day 42, patients with baseline CDSS score ≥6), and observed depression ($p<0.05$, Day 21, all patient population). **Conclusions:** ASE significantly improved a range of depressive symptoms in people with an acute exacerbation of schizophrenia, as measured by the CDSS. ASE may represent a beneficial treatment option for the management of depressive symptoms in patients with schizophrenia.

Key Words: Asenapine, Schizophrenia, Depression, Antipsychotic

[1]*St Vincent's Hospital and The University of Melbourne, Victoria, Australia*
[2]*H. Lundbeck A/S, Valby, Denmark*

Address for correspondence: David J. Castle, MD, Chair of Psychiatry, St Vincent's Hospital and The University of Melbourne, PO Box 2900 Fitzroy, Victoria 3065, Australia
Phone: +61-3-92884751; Fax: +61-3-92884802;
E-mail: david.castle@svhm.org.au

Submitted: March 31, 2014; Revised: August 17, 2014; Accepted: October 22, 2014

Introduction

It is well recognized that a substantial proportion of people with schizophrenia suffer from depression. In a review, Siris (1) estimated that full syndromic depression occurs with a modal rate of 25% in people with schizophrenia, but the risk of depression not meeting full syndromic criteria is much higher (2). Depression in schizophrenia is associated with adverse outcomes, including alcohol and other substance use and suicidality (3, 4).

It is thus of great concern that the evidence base for treatments of depression in schizophrenia is so limited. Specifically, few medications have been subjected to rigorous

Clinical Implications

We report here on change in depression symptoms in the context of schizophrenia in pooled data from three randomized controlled trials using the atypical antipsychotic asenapine (ASE). Depressive symptoms, as measured by the Calgary Depression Scale for Schizophrenia (CDSS), showed a greater reduction in ASE patients than those on placebo (PLA), at both Day 21 ($p<0.05$) and Day 42 ($p<0.01$) for the total patient population group, and at Day 21 ($p<0.05$) in patients with baseline CDSS total score ≥6. In terms of specific CDSS items, the core depressed mood item showed significant change from baseline in the ASE patients, compared to PLA, at Day 21 and at Day 42. Similar results were found for hopelessness (Day 21, patients with baseline CDSS ≥6), self-depreciation (Day 42, all patient population), guilty ideas of reference (Day 42, all patient population), pathological guilt (Day 21, all patient population; Day 21 and Day 42, patients with baseline CDSS score ≥6), and observed depression (Day 21, all patient population).

These data suggest an antidepressant effect of ASE in the context of acute schizophrenia. The results are synergistic with emerging data from trials of a number of other atypical antipsychotics, including olanzapine and quetiapine (2). We were not in a position to explore statistical differences between ASE and active comparators in the current study due to lack of statistical power and our primary comparison being with PLA. Further studies would be required specifically to investigate differences amongst antipsychotics regarding antidepressant effects.

testing in people with schizophrenia who are depressed. A Cochrane review (5) found eleven randomized controlled trials (total n=470) of antidepressants as adjuncts to antipsychotics in schizophrenia patients with depression. The authors concluded: "At present, there is no convincing evidence either to support or refute the use of antidepressants in treating depression in people with schizophrenia." Added to this lack of evidence is the potential for some antidepressants, notably imipramine (6), to worsen psychotic symptoms. Also, antidepressants have their own side effects such as sexual dysfunction that may exacerbate side effects of antipsychotics and reduce the likelihood of patient adherence. Finally, some antidepressants might have pharmacokinetic interactions with some antipsychotics and this may limit their use (2).

The so-called "atypical" antipsychotics have increasingly been seen as agents that have efficacy for mood symptoms. Hence, olanzapine (7, 8) and quetiapine (9-11) in particular are commonly used in clinical practice as mood stabilizers. Aripiprazole (12-14) has been used as an adjunct to antidepressants in major depressive disorder; and, quetiapine has been employed as both an adjunct (15) and as a solo agent (16-18) in major depression. Asenapine has an indication for acute mania and maintenance of bipolar mania.

In terms of depressive symptoms in schizophrenia itself, very few studies have been set up specifically to address this issue and most reports are post hoc analyses, often relying on mood rating scales that were not specifically designed to measure depression in schizophrenia.

Castle and Bosanac (2) have recently reviewed twenty-three studies of atypical antipsychotics in schizophrenia that measured changes in depression symptoms. Overall, there was a tendency for amelioration of depression with most agents studied, but the size of such effects was mostly modest and reliance was largely put on depressive subscores on measures such as the Brief Psychiatric Rating Scale (BPRS [19]) or the Positive and Negative Syndrome Scale (PANSS [20]). Only three of the reviewed studies used the "gold standard" depression rating scale for depression in schizophrenia, namely the Calgary Depression Scale for Schizophrenia (CDSS [21]), which takes account of the fact that negative symptoms can masquerade as depression. Thus, there is a need for further investigation of the effect of atypical antipsychotics in terms of antidepressant efficacy in schizophrenia.

Asenapine (ASE) is an atypical antipsychotic which has a pharmacological profile that would suggest that it would be effective for depressive symptoms. Functional receptor activity assays have revealed that ASE acts as an antagonist at a wide range of receptors, as it blocks agonist-induced activation of serotonin receptor types 1B, 2A, 2B, 2C, 6 and 7, and adrenergic receptors types 2A, 2B, and 2C, as well as dopamine D2 and histamine H1 receptors (22). Moreover, electrophysiological investigations suggest that the compound displays partial agonist activity at 5HT1A receptors (23). The functional outcomes of this broad pharmacological profile are believed to be an increase in dopamine, norepinephrine, and acetylcholine levels in cortical and limbic brain areas, and a potentiation of cortical glutamatergic neurotransmission; activities commensurate with antidepressant-like properties (24).

Hence, this paper reports a post hoc analysis of the effects of asenapine on depressive symptoms in schizophrenia.

Methods

Study Design

A post hoc analysis was performed on pooled data from three multinational, 6-week, Phase 3 studies that com-

Table 1 Baseline CDSS Total and Individual Item Scores for all Patients (n=914), and Patients with Baseline CDSS Total Score ≥6 (n=248)

	All Patients					Patients with Baseline CDSS Total Score ≥6				
CDSS	**ASE (n=427)**	**OLA (n=82)**	**HAL (n=97)**	**RIS (n=54)**	**PLA (n=254)**	**ASE (n=111)**	**OLA (n=20)**	**HAL (n=19)**	**RIS (n=23)**	**PLA (n=75)**
Total Score	**3.63**	**3.88**	**3.05**	**4.93**	**3.91**	**8.94**	**9.65**	**8.68**	**8.74**	**8.96**
Depression	0.75	0.74	0.75	0.81	0.76	1.53	1.65	1.95	1.30	1.52
Hopelessness	0.44	0.48	0.44	0.50	0.44	1.05	1.25	1.21	0.91	1.09
Self-depreciation	0.43	0.44	0.34	0.63	0.52	1.14	1.10	1.00	1.13	1.24
Guilty ideas of reference	0.38	0.45	0.29	0.52	0.41	1.04	0.90	0.79	0.91	1.01
Pathological guilt	0.33	0.46	0.25	0.63	0.42	0.95	1.20	0.68	1.17	0.99
Morning depression	0.40	0.32	0.31	0.61	0.41	0.98	0.95	0.84	1.04	1.00
Early wakening	0.41	0.48	0.32	0.54	0.43	1.03	1.20	0.74	1.04	0.84
Suicide	0.05	0.07	0.05	0.07	0.07	0.19	0.20	0.26	0.13	0.21
Observed depression	0.44	0.44	0.30	0.61	0.44	1.04	1.20	1.21	1.09	1.05

ASE=asenapine; OLA=olanzapine; HAL=haloperidol; RIS=risperidone; PLA=placebo.

pared fixed-dose asenapine (ASE; n=427), olanzapine (OLA; n=82), risperidone (RIS; n=54) or haloperidol (HAL; n=97) with placebo (PLA; n=254) in patients with schizophrenia in an acutely exacerbated state: Trial 1—Potkin et al. (25); trial 2—NCT00156117; and, trial 3—NCT00156104 and Kane et al. (26). A fourth multinational, 6-week, Phase 3 study (NCT00151424/HERA41022), using a flexible-dosing regimen, was not included in the present analysis.

Briefly, the trials included adult patients who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for a primary diagnosis of schizophrenia of the paranoid type, disorganized type, catatonic type, or undifferentiated type. The Positive and Negative Syndrome Scale (PANSS [20]) was used by the investigators to assess the severity of psychotic symptoms. Participants were required to have a PANSS score of at least 60 at screening and baseline (the baseline PANSS score could not have been ≥20% lower than the screening PANSS score); a score of at least 4 on two or more of the five items of the positive subscale of the PANSS at screening and baseline; and a Clinical Global Impression-Severity scale (CGI-S [27]) score of at least 4 ("moderately ill") at baseline. Patients were also required to have had a positive response to an antipsychotic medication other than clozapine, discontinued any depot neuroleptics prior to baseline, and provided written informed consent. Participants were excluded from the trial if they met *DSM-IV* diagnostic criteria for schizophrenia of residual subtype or schizoaffective disorder, or had a concurrent Axis I psychiatric disorder other than schizophrenia or a primary diagnosis other than schizophrenia. Suicidal patients were excluded from the trial.

Treatment

Patients were randomized to six weeks of double-blind PLA (sublingual + oral), sublingual ASE (10 or 20 mg, dose divided morning and evening) + oral PLA, oral OLA (15 mg) + sublingual PLA, oral RIS (6 mg, dose divided morning and evening) + sublingual PLA, or oral HAL (8 mg, dose divided morning and evening) + sublingual PLA (www.clinicaltrials.gov identifier/study ID/reference: not available/HERA41004/[25]; NCT00156117/HERA41021/not available; NCT00156104/HERA41023/[26]).

Outcome Measures

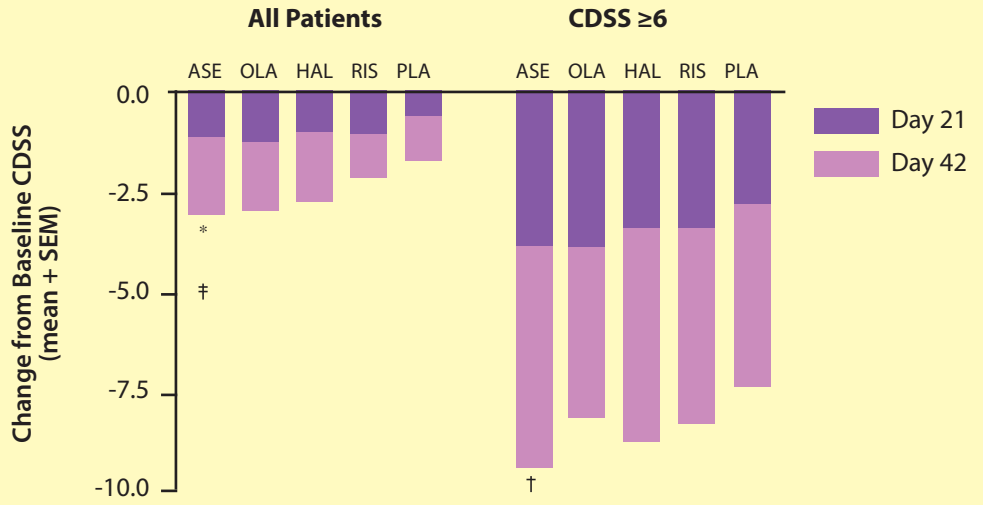
Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS [21]), at baseline, Day 21 and Day 42. For the purpose of the present analyses, the following patient groups were *a priori* defined:

- all patients, independent of baseline CDSS total score (n=914);
- patients with a baseline CDSS total score ≥6 (n=248), corresponding to 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode (28).

Statistical Analyses

The mean change from baseline CDSS total score and individual item scores was assessed at Day 21 and Day 42 in the total patient population (n=914), and in patients presenting with a CDSS total score of ≥6 at baseline (n=248). An MMRM (mixed model for repeated measurements) model was used to analyze change from baseline. Study as

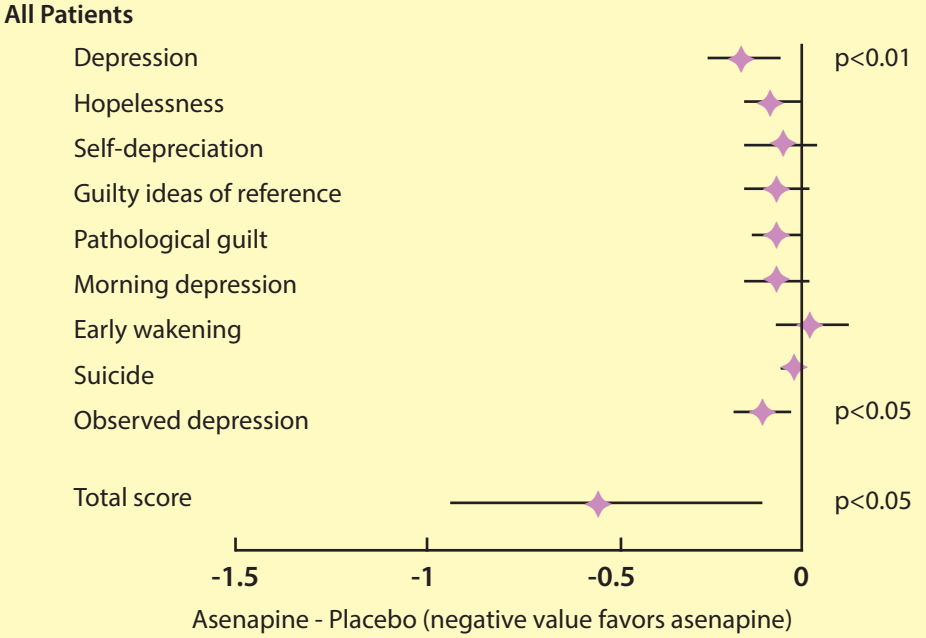
Figure 1 **Summary of Mean Changes from Baseline in CDSS Total Scores Induced by All Treatments at Day 21 and Day 42**



*p<0.05 versus PLA, Day 21; † p<0.05, ‡ p<0.01 versus PLA, Day 42.

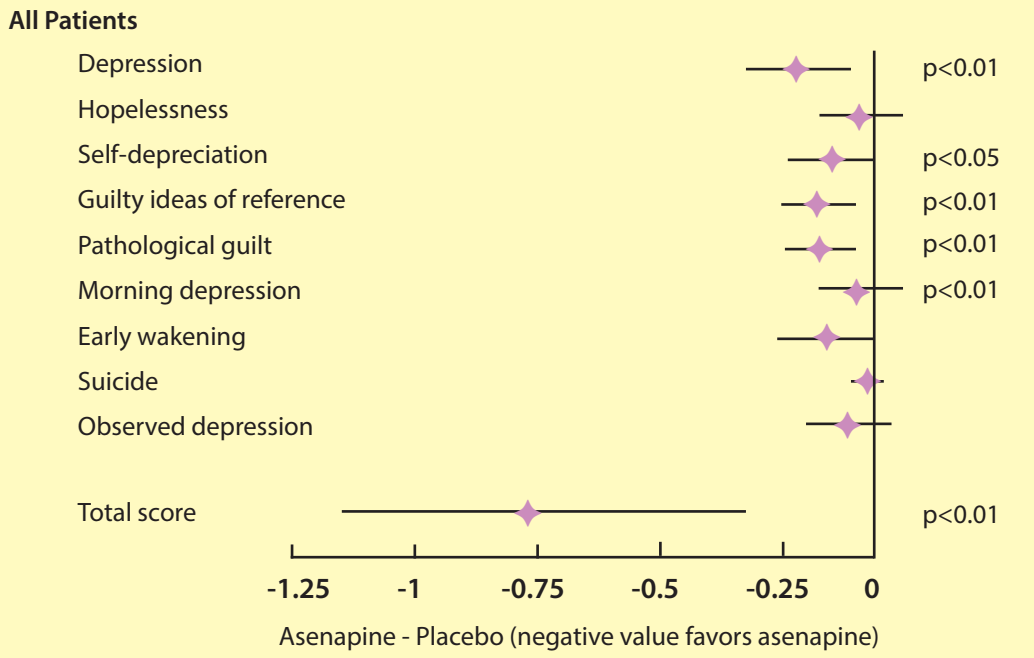
ASE: n=278 (all patients), n=66 (patients with baseline CDSS total score ≥6); HAL: n=66 (all patients), n=12 (patients with baseline CDSS total score ≥6); OLA: n=59 (all patients), n=14 (patients with baseline CDSS total score ≥6); RIS: n=26 (all patients), n=13 (patients with baseline CDSS total score ≥6); PLA: n=146 (all patients), n=46 (patients with baseline CDSS total score ≥6). *p<0.05 versus PLA, Day 21; †p<0.01 versus PLA, Day 42.

Figure 2 **The Effects of ASE (n=426) Versus PLA (n=254) on CDSS Total and Individual Item Scores Assessed at Day 21, for All Patients**



Full analysis set: treated patients with at least one post-baseline CDSS assessment.

Figure 3 The Effects of ASE (n=278) Versus PLA (n=146) on CDSS Total and Individual Item Scores Assessed at Day 42, for All Patients



Full analysis set: treated patients with at least one post-baseline CDSS assessment.

a factor, and the interactions between Baseline CDSS Score and Study Day and between Treatment and Study Day were included in the model. The difference between ASE and PLA at Days 21 and 42 was deducted from the Treatment and Study Day interaction.

Results

Patient characteristics of two of the three primary studies included in the present analyses have been published elsewhere (25, 26). Briefly, baseline clinical characteristics were comparable between the treatment groups within each study and in the pooled dataset. Of the 914 patients (male: 64.4%, female: 35.6%) included in the present pooled analyses, 427 patients (46.7%) were treated with ASE, 254 (27.8%) with PLA, 54 (5.9%) with RIS, 82 (9.0%) with OLA, and 97 (10.6%) with HAL. Most patients were aged 18 to 64 years (98.9%) and over half were Caucasian (53.4%), with the remainder of patients being Black (35.4%), Asian (5.5%), or other (5.7%). The average PANSS total scores at baseline was comparable across treatment groups (ASE: 91.2, PLA: 91.0, RIS: 92.0, OLA: 93.5, HAL: 88.4). Baseline CDSS total scores and individual item scores, for all patients and patients with baseline CDSS total score ≥6, are shown in Table 1. Overall, the scores reflected a patient sample suffering mild depressive symptoms, in accordance with the primary aim of the original studies, i.e., registrational trials for ASE in schizophrenia (see Study Design section above).

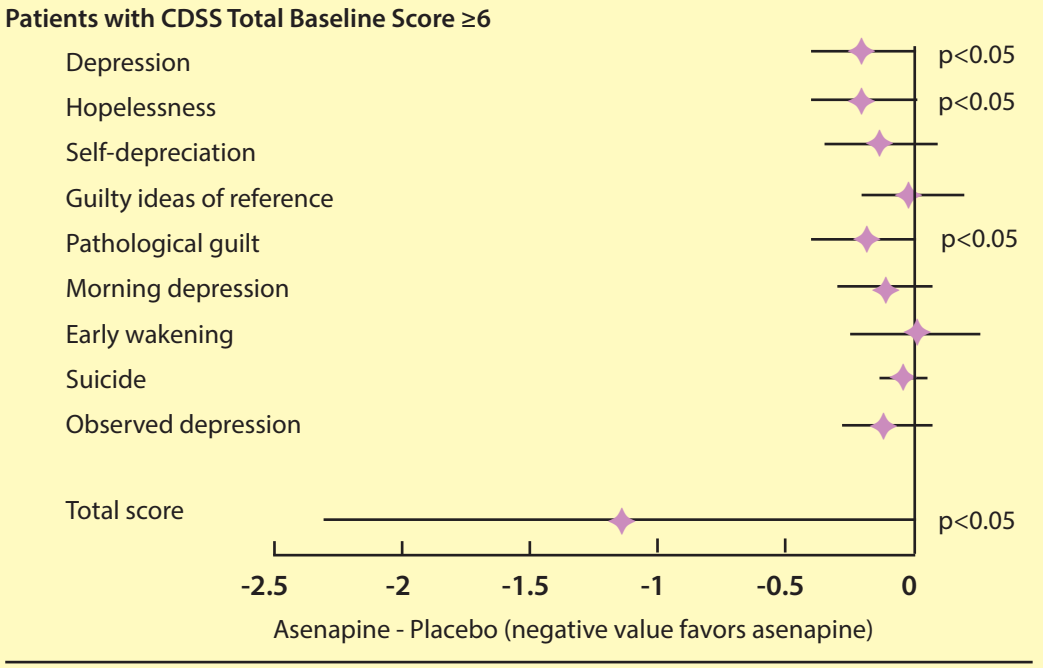
A summary of the effects of all treatments on CDSS total scores at Day 21 and Day 42 in all patients, and in patients with a baseline CDSS score ≥6, is shown in Figure 1.

In brief, ASE treatment induced a significant change from baseline in CDSS total score (-1.15±0.15) at Day 21 ($p<0.05$, versus PLA: -0.61±0.18), and at Day 42 (-1.84±0.15; $p<0.01$, versus PLA: -1.09±0.20) for the total patient population group. In patients with a baseline CDSS total score ≥6, ASE induced a significant change from baseline at Day 21 (-3.99±0.38; $p<0.05$, versus PLA: -2.85±.45), but not at Day 42 (-5.49±0.42, versus PLA: -4.53±0.49).

Analysis of individual item CDSS scores at Day 21 (shown in Figure 2) for all patients revealed significant changes from baseline in CDSS depression score with ASE treatment (-0.26±0.03; $p<0.01$, versus PLA: -0.10±0.04). In addition, ASE significantly improved CDSS observed depression score (-0.11±0.03; $p<0.05$, versus PLA: -0.01±0.03). Effects of ASE on all other CDSS individual item scores were comparable with placebo.

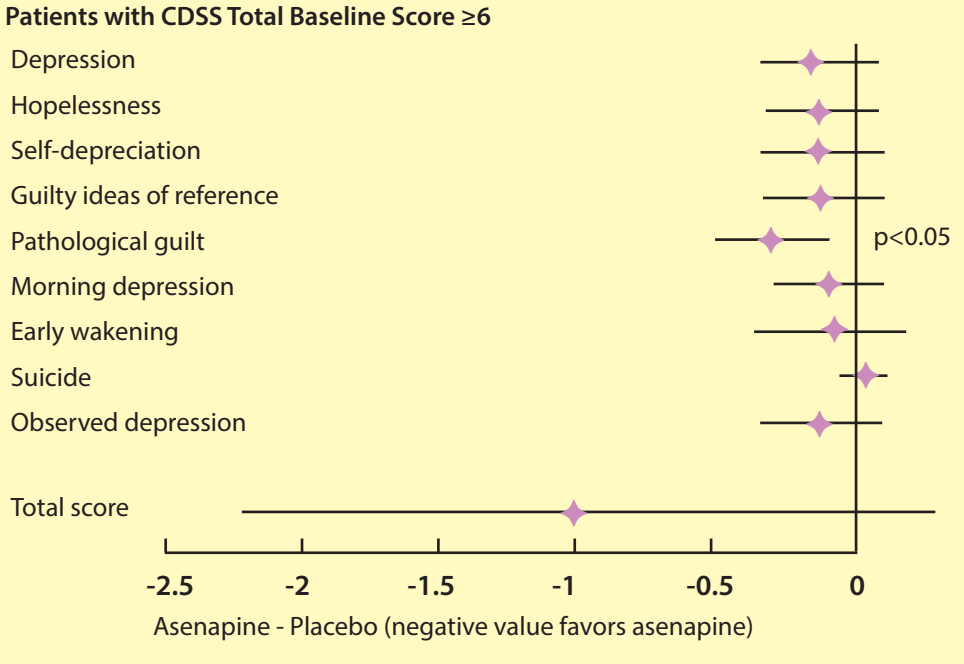
Analysis of individual item CDSS scores at Day 42 (shown in Figure 3) for all patients revealed significant changes from baseline in CDSS depression (-0.36±0.04; $p<0.01$, versus PLA: -0.19±0.05), self-depreciation (-0.24±0.03; $p<0.05$, versus PLA: -0.14±0.04), guilty ideas of reference (-0.26±0.03; $p<0.01$, versus PLA: -0.13±0.03), and pathological guilt (-0.26±0.03; $p<0.01$, versus PLA: -0.14±0.03) associated with ASE treatment. Effects of ASE on hopelessness, morning

Figure 4 The Effects of ASE (n=111) Versus PLA (n=75) on CDSS Total and Individual Item Scores Assessed at Day 21, for Patients with a Baseline CDSS Total Score of ≥6



Full analysis set: treated patients with at least one post-baseline CDSS assessment.

Figure 5 The Effects of ASE (n=66) Versus PLA (n=46) on CDSS Total and Individual Item Scores Assessed at Day 42, for Patients with a Baseline CDSS Total Score of ≥6



Full analysis set: treated patients with at least one post-baseline CDSS assessment.

depression, early wakening, and suicidal ideation CDSS individual item scores were statistically comparable with PLA.

Analysis of individual item CDSS scores in patients with a baseline CDSS score ≥6 at Day 21 (shown in Figure 4) revealed significant changes from baseline in CDSS depression score (-0.68±0.07; $p<0.05$, versus PLA: -0.46±0.08), as well as hopelessness (-0.53±0.07; $p<0.05$, versus PLA: -0.33±0.08), and pathological guilt (-0.55±0.06; $p<0.05$, versus PLA: -0.35±0.08) following ASE treatment. The effects of ASE on all other CDSS individual item scores were statistically comparable with PLA.

ASE treatment induced a significant improvement in CDSS pathological guilt score (-0.76±0.07) at Day 42 ($p<0.05$, versus PLA: -0.51±0.09) in patients with a baseline CDSS total score of ≥6 (shown in Figure 5). The effects of ASE on CDSS total score and all other individual item scores were comparable with PLA.

Discussion

We report here on change in depression symptoms in the context of schizophrenia in pooled data from three randomized controlled trials using the atypical antipsychotic ASE. Depressive symptoms, as measured by the CDSS, showed a greater reduction in ASE patients than those on PLA, at both Day 21 ($p<0.05$) and Day 42 ($p<0.01$) for the total patient population group, and at Day 21 ($p<0.05$) in patients with baseline CDSS total score ≥6. In terms of specific CDSS items, the core depressed mood item showed significant change from baseline in the ASE patients, compared to PLA, at Day 21 and at Day 42. Similar results were found for hopelessness (Day 21, patients with baseline CDSS ≥6), self-depreciation (Day 42, all patient population), guilty ideas of reference (Day 42, all patient population), pathological guilt (Day 21, all patient population; Day 21 and Day 42, patients with baseline CDSS score ≥6), and observed depression (Day 21, all patient population).

These data suggest an antidepressant effect of ASE in the context of acute schizophrenia. The results are synergistic with emerging data from trials of a number of other atypical antipsychotics, including olanzapine and quetiapine (2). We were not in a position to explore statistical differences between ASE and active comparators in the current study due to lack of statistical power and our primary comparison being with PLA. Further studies would be required specifically to investigate differences amongst antipsychotics regarding antidepressant effects.

Limitations

Our results need to be interpreted in the light of the fact that this was a post hoc series of analyses based on pooled data from studies that were not specifically set up to test antidepressant effects. In this context, patients were selected such that they would not have prominent depressive symptoms; and, active suicidality was an exclusion criterion. These latter factors reduced our chances of finding significant changes in the CDSS due to floor effects and small numbers of patients with a CDSS ≥6, especially at Day 42 (which is perhaps why there was a null result at Day 42 for this group); and, also limit the generalizability of the data in terms of the broader clinical population of people with schizophrenia, in whom depression is all too common (29). The studies were acute phase studies of limited duration, albeit the time frame of the studies was sufficient to observe antidepressant effects. The importance of longer-term studies cannot be understated as depressive symptoms accompanying an acute psychotic episode have different clinical implications from longer-term depression after the resolution of the acute episode.

These caveats aside, the study has the strengths of rigorous design and methodology and the use of the "gold standard" CDSS, specifically designed for use in schizophrenia populations in that it reduces confounding effects of negative symptoms in particular. Furthermore, we did see consistent changes across the items in the CDSS, including the core depressed mood item.

Conclusions

In conclusion, this post hoc analysis provides evidence of antidepressant effects of ASE in acute exacerbations of schizophrenia. Further studies designed specifically to assess depression in schizophrenia, with sufficient statistical power and longer-term outcomes, will be required to more definitively determine the status of this agent in this context.

Acknowledgments

J.P. Redrobe and J.K. Simonsen (affiliated to H. Lundbeck A/S) provided support in the preparation, revision and editing of the methods and results sections of the manuscript.

Disclosures

David Castle has received grant monies for research from Eli Lilly, Janssen Cilag, Roche, Allergen, Bristol-Myers Squibb, Pfizer, Lundbeck, Astra Zeneca, Hospira; Travel Support and Honoraria for Talks and Consultancy from Eli Lilly, Bristol-Myers Squibb, Astra Zeneca, Lundbeck, Janssen Cilag, Pfizer, Organon, Sanofi-Aventis, Wyeth, Hospira, Servier; and is a current or past Advisory Board Member for Lu AA21004: Lundbeck; Pristiq: Pfizer; Varenicline: Pfizer; Asenapine: Lundbeck; Seroquel: Astra Zeneca; Bitopertin: Roche; Aripiprazole LAI: Lundbeck. He has no stocks or shares in any pharmaceutical company.

References

1. Siris SG. Depression in schizophrenia: perspective in the era of "Atypical" antipsychotic agents. Am J Psychiatry 2000;157(9):1379-1389.
2. Castle D, Bosanac P. Depression and schizophrenia. Advances in Psychiatric Treatment 2012;18:280-288.
3. Ross S, Peselow E. Co-occurring psychotic and addictive disorders: neurobiology and diagnosis. Clin Neuropharmacol 2012;35:235-243.
4. Mauri MC, Paletta S, Maffini M, Moliterno D, Altamura AC. Suicide attempts in schizophrenic patients: clinical variables. Asian J Psychiatr 2013:6(5);421-427.
5. Furtado VA, Srihari V. Atypical antipsychotics for people with both schizophrenia and depression. Cochrane Database Syst Rev 2008 Jan 23;(1):CD005377.
6. Siris SG, Bermanzohn PC, Mason SE, Shuwall MA. Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. Arch Gen Psychiatry 1994;51(2):109-115.
7. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60(1):1079-1088.
8. Vieta E, Locklear J, Günther O, Ekman M, Miltenburger C, Chatterton ML, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. J Clin Psychopharmacol 2010;30(5):579-590.
9. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162(7):1351-1360.
10. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26(6):600-609.
11. Suppes T, Vieta E, Liu S, Brecher M, Paulsson B; Trial 127 Investigators. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry 2009;166(4):476-488.
12. Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, Alpert JE, et al. Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. J Clin Psychiatry 2005;66(10):1326-1330.
13. Patkar AA, Peindl K, Mago R, Mannelli P, Masand PS. An open-label, rater-blinded, augmentation study of aripiprazole in treatment-resistant depression. Prim Care Companion J Clin Psychiatry 2006;8(2):82-87.
14. Steffens DC, Nelson JC, Eudicone JM, Andersson C, Yang H, Tran QV, et al. Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. Int J Geriatr Psychiatry 2011;26(6):564-572.
15. Dannlowski U, Baune BT, Böckermann I, Domschke K, Evers S, Arolt V, et al. Adjunctive antidepressant treatment with quetiapine in agitated depression: positive effects on symptom reduction, psychopathology and remission rates. Hum Psychopharmacol 2008;23(7):587-593.
16. Cutler AJ, Montgomery SA, Feifel D, Lazarus A, Aström M, Brecher M. Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. J Clin Psychiatry 2009;70(4):526-539.
17. McIntyre RS, Muzina DJ, Adams A, Lourenco MT, Law CW, Soczynska JK, et al. Quetiapine XR efficacy and tolerability as monotherapy and as adjunctive treatment to conventional antidepressants in the acute and maintenance treatment of major depressive disorder: a review of registration trials. Expert Opin Pharmacother 2009;10(18):3061-3075.
18. Weisler R, Joyce M, McGill L, Lazarus A, Szamosi J, Eriksson H; Moonstone Study Group. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. CNS Spectr 2009;14(6):299-313.
19. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychological Reports 1962;10:799-812.
20. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-276.
21. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. Schizophr Res 1990;3(4):247-251.
22. Shahid M, Walker GB, Zorn SH, Wong EH. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. J Psychopharmacol 2009;23(1):65-73.
23. Ghanbari R, El Mansari M, Shahid M, Blier P. Electrophysiological characterization of the effects of asenapine at 5-HT(1A), 5-HT(2A), alpha(2)-adrenergic and D(2) receptors in the rat brain. Eur Neuropsychopharmacol 2009;19(3):177-187.
24. Tarazi FI, Neill JC. The preclinical profile of asenapine: clinical relevance for the treatment of schizophrenia and bipolar mania. Expert Opin Drug Discov 2013;8(1):93-103.
25. Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. J Clin Psychiatry 2007;68(10):1492-1500.
26. Kane JM, Cohen M, Zhao J, Alphs L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. J Clin Psychopharmacol 2010;30(2):106-115.
27. Guy W. ECDEU Assessment Manual for Psychopharmacology Revised. (Publication ADM 76-338) US Department of Health, Education, and Welfare; Rockville, MD; 1976; p. 218-222.
28. Addington D, Addington J, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993;(22):39-44.
29. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull 2009;35(2):383-402.